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SPECIAL ISSUE: ARTHRITIS

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News&Features from NIH

February 1983

NIH intramural scientists are using several different approaches in studying the various types of arthritis. Animal models are used to provide information and several clinical trials are being conducted. Studies include work on the antigen/antibody complexes in the inflammatory process. For patients with severe rheumatoid arthritis, treatment by a process called leukapheresis to reduce inflammation is being investigated.

Both laboratory and clinical studies are also being conducted on systemic lupus erythematosus and the role of genetic factors in this condition. See page 6

The causes and cure of rheumatoid arthritis have eluded scientists. Recently, however, NIH studies have shown that Epstein-Barr virus (EBV), the organism that causes infectious mononucleosis, may trigger the development of rheumatoid arthritis in patients genetically predisposed to the disease.

Although the causes of rheumatoid arthritis are multifactorial, the formulation of an EBV vaccine could one day prevent some susceptible patients from contracting this condition. See page 5

Five hundred thousand people in the U.S. have systemic lupus erythematosus, a potentially serious inflammatory disease of the connective tissue. NIADDK supports many diverse intramural and extramural research projects on the causes and treatment of lupus.

Studies include investigation of neurological involvement; kidney impairment; the significance of genetic factors; the role of antigens and antibodies in the immunological process; and estrogen metabolism abnormalities in patients with lupus. See page 8

NIADDK currently supports 20 Centers throughout the country whose purpose is to increase the existing body of knowledge about arthritis by fostering development of new data and improving the application of current information.

These Multipurpose Arthritis Centers (MACs) conduct programs in basic and clinical research; professional, patient and public education; and community projects and health services research.

One study, at a MAC in Boston, is investigating total irradiation of the lymph nodes in the treatment of severe rheumatoid arthritis.

At a California MAC, studies are being conducted on the potential of this procedure for patients with systemic lupus erythematosus.

Other MAC projects include studying the cost effectiveness of joint replacement surgery; care for home-bound patients; and the problems of children with arthritis. See page 10

Cover photo courtesy
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Arthritis Advisory Board

Editorial Staff

Susan Gerhold
Acting Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

NIH News Branch
Building 31, Room 2B-10
Bethesda, Maryland 20205

Phone:
(301) 496-2535

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Arthritis Research Update: Progress Against Disorders that Afflict Millions

Connie Raab

"Arthritis." To some it is the "minor aches and pains" for which people on television commercials take aspirin. For others, the word conjures up fearful images of pain and crippling. Many people associate arthritis with growing older.

Arthritis can be all of these—and much more. The word literally means "joint inflammation," but to scientists and physicians and a growing number of knowledgeable consumers, the term refers to a broad family of over 100 rheumatic diseases and related disorders. These disorders can affect not only the joints, but the connective tissues—the supporting tissues of the body such as muscles, tendons, and ligaments, and the protective coverings of internal organs.

According to 1980 data, at least 35 million Americans—about one in seven—have some form of arthritis. If related musculoskeletal disorders are included, many believe the number tops 39 million.

Most forms of arthritis are chronic. "Many patients face such long-term problems as unemployment, emotional stress, and the financial burden of extended medical care," says Dr. Lawrence E. Shulman, Director of the Division of Arthritis, Musculoskeletal and Skin Diseases of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). The economic impact of arthritis and rheumatic diseases is about $14 billion per year, according to current estimates by the Arthritis Foundation.

The rabbit is used as an animal model for osteoarthritis, a common form of arthritis in which the joint cartilage wears away. Using this model, NIADDK-supported scientists at Case Western Reserve University in Cleveland are studying biochemical and cellular changes in cartilage as the disease progresses and are working towards developing new therapies.

NIH PHOTO 1824

A Diverse Group of Disorders

Each form of arthritis is unique; each has different causes, symptoms and patterns. The most prevalent forms are described in this special issue.

Osteoarthritis (OA), sometimes called the "wear and tear disease," can affect the hips, knees, spine and the end joints of the fingers. In OA there is a breakdown of joint cartilage, followed by bony overgrowth at the edges of the joint, often making movement painful.

Rheumatoid arthritis (RA) is the disorder many people think of as "arthritis." Its hallmark is inflammation, which causes heat, swelling, and pain in both large and small joints. RA can also lead to weakness, fatigue, loss of appetite and stiffness. The disease tends to be chronic, disabling and irregular—the patient can feel good one day and awful the next.

Gout or *gouty arthritis* is a disorder that results when excess uric acid, a body chemical, forms in crystals in the joints causing inflammation and what some call "exquisite" pain.

Systemic lupus erythematosus (SLE or *lupus)* causes arthritis and a skin rash early on and can later strike various internal organs such as the kidneys, heart and brain. In lupus, the immune or defense system seems to attack the body's own tissues.

Juvenile arthritis (JA), as the name implies, afflicts children. JA is thought to encompass several disease states that differ according to the joints involved, severity, age of onset, and complications. The complications of JA can include growth retardation, crippling and, in one of ten children with arthritis, iritis, or inflammation of the iris of the eye possibly leading to blindness.

Ankylosing spondylitis or spinal arthritis causes back pain, stiffness, and loss of spinal mobility and can lead to fusion and rigidity of the vertebrae.

Scleroderma or *progressive systemic sclerosis* is a disorder of the connective tissue, with abnormality of the fine blood vessels. Scleroderma can cause thickening and hardening of the skin and can also afflict the gastrointestinal system, heart, lungs, and kidneys.

A National Focus on Arthritis Research

NIADDK is the primary focus in the Federal effort to combat the many forms of arthritis. Through grants and contracts of the extramural Division of Arthritis, Musculoskeletal and Skin Diseases, NIADDK supports investigators at universities, medical schools and other research institutions across the United States. The Institute also conducts an intensive program of arthritis research on the campus of the NIH, through the intramural Arthritis and Rheumatism Branch.

Arthritis is not just a disease of the elderly. People of all ages can develop arthritis, and the Arthritis Foundation estimates that as many as a quarter of a million children under age 16 have some form of arthritis. (Photo courtesy of the National Arthritis Advisory Board.)

NIH PHOTO 1825

Some NIADDK-supported research studies are clinical and focus specifically on observations of patients with various forms of arthritis. A smaller amount of research is devoted to epidemiological studies, which measure and analyze how a disease is distributed in a given population and which help identify factors associated with the disease. However, more than half of the arthritis research funded by the Institute is fundamental or "basic" research, which takes place in laboratories, and sometimes is aided by animal models to investigate diseases that afflict humans.

Advances in basic research can enable investigators to understand why a disease occurs, why and how it might progress, and what might be changed to prevent it from occurring or to arrest it when it does occur.

Research investigators in a wide variety of disciplines are exploring the factors that underlie the forms of arthritis. This variety in disciplines is partly because the diseases are so varied in their expression and partly because many of the individual diseases seem to result from a combination of factors. Several areas of basic arthritis research have yielded important new information.

Immunology—Immunity is the body's capacity to distinguish self from nonself, or foreign matter, and to eliminate or neutralize the latter. However, some rheumatic diseases, notably lupus and rheumatoid arthritis, are often called "autoimmune diseases," because it seems as if the immune system is reacting against the patient's own tissues. "Autoimmunity is not a good explanation," says Dr. John Decker, chief of the NIADDK Arthritis and Rheumatism Branch. "It is more accurate to say that in rheumatoid arthritis, for example, there is an immunological disturbance and reactivity against some undetected antigen or antigens."

There are two interrelated aspects of the immune system; one involves antibodies (huge protein molecules known as immunoglobulins) and the other involves certain cells. The term "humoral immunity" refers to the first aspect, in which specific antibodies are formed in response to specific antigens (substances which provoke the immune response). These circulate in the blood and other body fluids, suggesting the derivation of the term from ancient circulating humors.

The second aspect of the immune system, referred to as "cellular immunity," is becoming more and more important to the study of the rheumatic diseases. A variety of cells may become "sensitized" to specific antigens. These include: B lymphocytes (B cells), which are a precursor of the cells which produce antibodies; T lymphocytes (T cells) which induce or suppress antibody formation and are responsible for much of cellular immunity; and monocytes which are transformed to macrophages and get rid of cells and foreign particles by engulfing them.

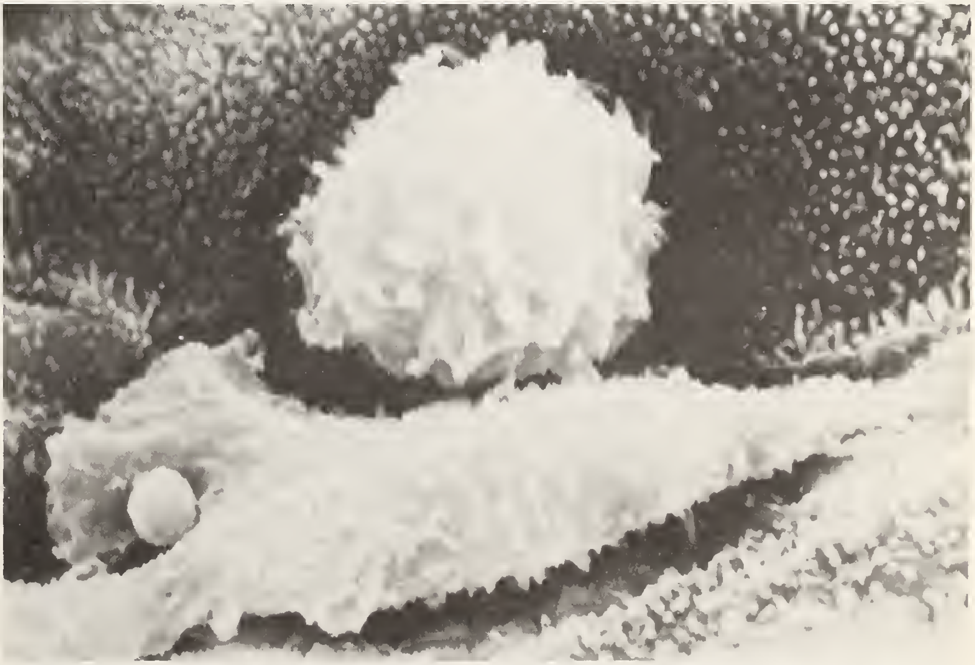
Immunity is also governed by a complicated (and not fully understood) sequence of events, which includes numerous chemicals and factors. Many investigators feel one key to treating such conditions as rheumatoid arthritis is to manipulate the immune system, to find drugs or techniques that interfere with the functions or products of the cells of the immune system.

Some available therapies, such as many of the common arthritis drugs, interrupt the immuno-inflammatory cycle, although they do not seem to affect the underlying disease mechanism. Other drugs, usually reserved for more severe cases of RA and other diseases, are broadside attacks on the immune system, which have toxic side effects. Some examples are immunosuppressive drugs, such as methotrexate, cyclophosphamide and azathioprine. In addition to drugs, certain techniques are also being explored. For example, irradiation of the lymph system, normally used to treat certain cancers, seems, by combating an abnormality of the immune system, to reduce joint inflammation in patients with severe RA (see January 1982 *News and Features.*)

Another promising technique is apheresis, a sort of "blood washing" method that removes cells or other blood components that might be promoting a particular disorder. NIADDK is sponsoring a trial which tests therapy for lupus kidney disease by plasmapheresis, in which the patient's "diseased" plasma is replaced by fresh plasma or a plasma substitute (see October 1982 *News and Features*). NIADDK's intramural Arthritis and Rheumatism Branch is evaluating therapy

One important focus of arthritis research is the development of more effective drug therapy. These NIADDK grantees at Florida A&M University in Tallahassee are working to develop modified forms of corticosteroids which have the benefits of corticosteroids with fewer risks. (Photo courtesy of M. Mitchell.)

NIH PHOTO 1826



This scanning electron micrograph shows two macrophages. The macrophage at the bottom is about to devour a foreign particle. (Micrograph courtesy of the National Heart, Lung, and Blood Institute.)

NIH PHOTO 1827

continued on next page

of severe rheumatoid arthritis by leukapheresis, which removes white blood cells (see this issue).

Inflammation—when some antigen—whether it is a foreign substance or for some reason the body tissue—provokes an immune response, a complex sequence of events, which includes numerous chemicals and factors, brings plasma proteins and sensitized cells into the area. The result is inflammation, the redness, swelling, heat, and pain, typical of a cut on the arm as well as a swollen joint. The inflammatory process is a beneficial defense mechanism which gets rid of the offending substance and enables tissue repair. In the case of rheumatoid arthritis and related diseases, however, it becomes a seemingly nonstop cycle of events that can cause damage to the joints and surrounding tissues, and in some cases cause deformity and loss of function.

Investigators are beginning to better understand inflammation. For example, they have found that certain enzymes that destroy tissue are released due to inflammation, and that process is influenced by substances known as prostaglandins. The complicated production pathway of prostaglandins has been clarified only in the past decade, and, in fact, the 1982 Nobel prize for medicine was awarded for elucidation of the prostaglandins. It is now known that common arthritis agents, such as aspirin, block this pathway. Another set of substances, the leukotrienes, is just beginning to be understood; these seem to have an even more powerful influence on inflammation than do prostaglandins. Researchers are intensely searching for drugs that block the effects of these substances.

Infectious triggers—Many scientists believe that environmental agents may set off certain rheumatic diseases such as rheumatoid arthritis, perhaps in genetically susceptible individuals. They are studying a whole host of possible viruses, bacteria and other organisms, such as mycoplasma.

Indeed, infectious or septic arthritis has long been recognized as joint inflammation arising from a primary infection elsewhere in the body. Some types can be "cured" if the infection is treated effectively. Examples are gonococcal, staphylococcal, tubercular or streptococcal infection.

Lyme arthritis was discovered by NIADDK grantees at Yale University in 1976 and later traced to a tick bite. In 1982 it was reported to be related to a specific spirochete (bacteria) found in the tick (see the June/July issue of *News and Features.*)

Some investigators believe a "latent virus hypothesis,"—that some virus-like substance lies dormant in the body for a long period of time and then for some unknown reason sets off the body's immune system to cause an inflammatory reaction. For example, important recent findings have shown an association between the EB virus (which causes infectious mononucleosis) and rheumatoid arthritis (see this issue).

Lyme arthritis is thought to be caused by an infectious agent transmitted by ticks of the *Ixodes* genus; in the East, *Ixodes dammini* (above) and in the West *Ixodes pacificus.* (Photo courtesy of Dr. A. Spielman.)

NIH PHOTO 1828

Other promising areas of basic arthritis research include: *Studies of cartilage structure and metabolism*—Cartilage cushions the ends of bones which meet to form the joints. It seems cartilage does not repair itself well when damaged by chronic inflammation or injury. The reasons for this are currently being examined.

Several enzymes with tissue-eroding potential have been isolated from cartilage. The tissue destruction observed in various joint disorders may be related to the release or activation of these enzymes. Some researchers are trying to relate the release of enzymes to biomechanical forces (a major factor in the development of osteoarthritis, the most common form of arthritis).

Epidemiology and genetics—Population studies have shown an association between several of the rheumatic diseases and genetic tissue markers known as HLA antigens (certain inherited molecules on cells that determine the rejection of organ transplants, such as the kidneys). One quite striking association was discovered in the early seventies, that 90 percent of people with ankylosing spondylitis have the marker known as HLA-B27 whereas this marker occurs in only 8 percent of populations free of the disease. Since then, weaker associations have been found between various HLA antigens and such conditions as rheumatoid arthritis, lupus, Sjögren's syndrome, psoriatic arthritis, and certain subgroups of juvenile arthritis. These genetic markers may enable the identification of individuals at risk for these diseases and can help distinguish different forms of a disorder such as juvenile arthritis.

Metabolism of toxic body products—Certain forms of arthritis, notably gout, occur when excessive amounts of body chemicals are deposited in the joints. Gout is apparently an inherited disorder of purine metabolism. Purines are metabolized to uric acid and are excreted in the urine. In the past two decades, researchers have shown that the formation of needle-like crystals from uric acid causes the pain of gout, and they have found drugs that can keep gout completely under control. However, they ar still trying to determine the factors responsible for the formation of these crystals and to understand why some, but not all, people with high levels of uric acid develop gout.

Biomaterials and joint prosthetics—Some of the most remarkable progress in arthritis research has been in the area of biomaterials and joint prostheses. Hips, knees, finger joints, wrists, and other joints severely damaged by disease or injury can be replaced by artificial joints made of plastics, metals, and other "biomaterials" specially fabricated to be long-lasting and compatible with body tissues. Joint replacement can, in many cases, greatly relieve pain and restore much of lost function.

However, a major cause of joint replacement failure is that sometimes the joint replacements loosen from the bone in which they are implanted within several years.

While improved cement and better cementing techniques have improved to some degree, a more permanent attachment with bone ingrowth may be the best solution.

This is an area of intense research, with NIADDK grantees and other researchers developing experimental joint replac ments with porous coatings or speci surface finishings which may encourage the bone to grow into the replacement.

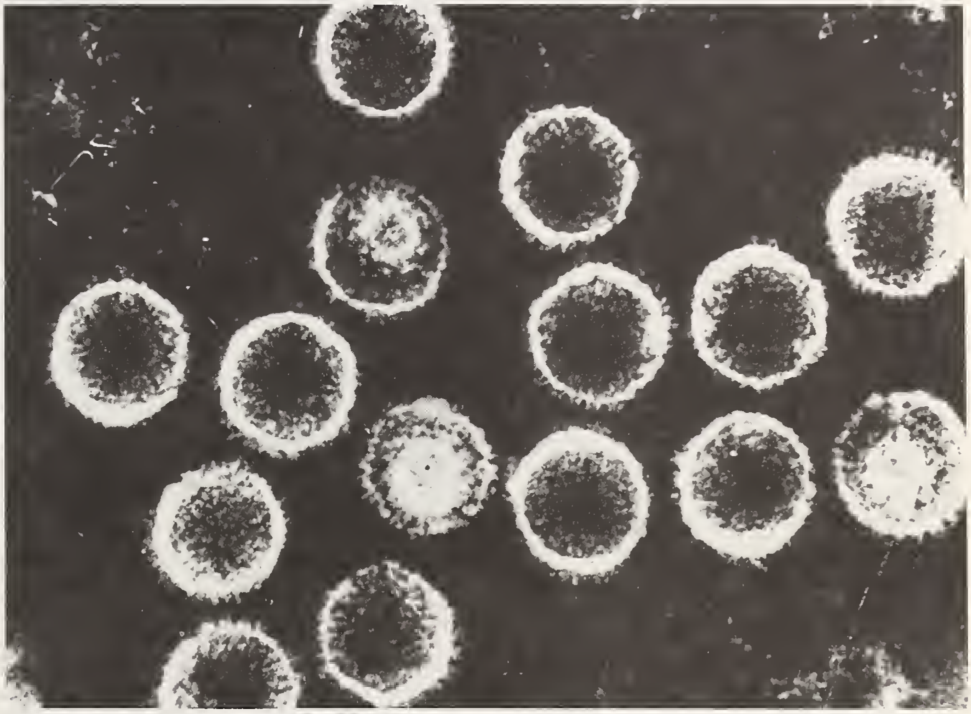
Advances in these basic areas of research are enabling investigators to improve methods of diagnosis, to look for effective new anti-arthritis drugs and to refine the use of older medications, to develop better ways to surgically correct joints damaged by arthritis, and to find new, experimental types of therapy for the many forms of arthritis. ■

Fundamental research conducted and supported by NIADDK is providing important clues to the causes and development of many forms of arthritis.

NIH PHOTO 1829

Mononucleosis and Rheumatoid Arthritis: Is There a Common Culprit?

Linda Stalvey



The Epstein-Barr virus is the infamous cause of the "kissing disease," mononucleosis. It may also help cause rheumatoid arthritis in some people. (Photo courtesy Dr. Guy de Thé and *Medical World News*.)

NIH PHOTO 1830

Rheumatoid arthritis, a disease characterized by joint inflammation, affects 6.5 million people in the United States. Inflammation and thickening of the tissue lining the joints causes pain and swelling for the arthritis victim. If uncontrolled, rheumatoid arthritis can lead to deformity and eventually, disability. Arthritis varies widely from person to person, however, and while the disease can be mild in one person, it can cripple another.

The disease has generated a great deal of study over the years, but to date the cause and cure of rheumatoid arthritis have remained elusive.

Recent work performed by NIH intramural scientists Dr. Alfred Steinberg of the NIADDK, and Drs. Giovanna Tosato and Michael Blaese of the National Cancer Institute (NCI), has shown an association between a particular viral infection and rheumatoid arthritis.

This exciting research finding proposes not only a possible trigger of rheumatoid arthritis, but also indicates a possible means for prevention. If rheumatoid arthritis is set off by a particular viral infection in some people, it may be possible to produce a vaccine and immunize populations at risk for developing the disease. This line of investigation is currently being followed by several different investigators.

Epstein-Barr virus, or EBV, is the organism that causes infectious mononucleosis. By young adulthood, most people have antibodies to EBV in their blood, indicating prior infection. For many the infection is asymptomatic. Patients with rheumatoid arthritis have more of these EBV antibodies in their blood than individuals without rheumatoid arthritis.

Once an individual is infected with EBV, the virus remains within a specific group of white blood cells, called B lymphocytes or B cells, for several years, perhaps for life.

By studying the interactions of EBV and white cell function in patients with rheumatoid arthritis, the NIH scientists hope to explain a possible cause of the disease.

Cell cultures of lymphocytes from individuals not suffering from rheumatoid arthritis but who have had an EBV infection, produce antibodies or immunoglobulins when they are re-exposed to the virus. After about 12 days the normal cells stop producing immunoglobulins. This suppression of immunoglobulin production is mediated by a separate set of white blood cells, the T lymphocytes or T cells. The cells from patients with rheumatoid arthritis continue to produce immunoglobulins; their T cells fail to suppress the immunoglobulin production by their B cells.

This apparent T cell defect, a failure to suppress antibody production in rheumatoid arthritis patients, led the researchers to postulate that this virus was responsible for some of the immune abnormalities expressed in rheumatoid arthritis.

T cell function was also examined in patients with other immune disorders, such as systemic lupus erythematosus and scleroderma. The defect was not evident in these patients.

Rheumatoid arthritis patients also display other EBV-related phenomena. They have a high frequency of a nuclear antigen called RANA, which is relatively uncommon in those free of the disease; greater amounts of antibodies to a variety of EBV-associated antigens; and their lymphocytes will transform much more readily into "immortal" cells.

These observations indicate that EBV may play a role in the immunological features of rheumatoid arthritis. Moreover, EBV-infected B cells produce substantial amounts of rheumatoid factor, an autoantibody found in many patients with rheumatoid arthritis. While a majority of patients show an enhanced immune response to EBV, not all rheumatoid arthritis patients do.

Rheumatoid arthritis appears to be a disease of multifactorial causes, some of them probably genetic. Based on these and other observations, it can be hypothesized that only those patients genetically predisposed to rheumatoid arthritis will develop the disease when it is triggered by EBV.

The work of Steinberg, Tosato, and Blaese eventually may have important implications in the treatment and prevention of rheumatoid arthritis. If the regulatory mechanism to control the EBV-infected B cells and to prevent their excessive immunoglobulin production can be found, it may be possible to return the rheumatoid arthritis patient to normal immune function. More importantly, if an EBV vaccine can be developed, the trigger for rheumatoid arthritis in a portion of the susceptible patient population could be eliminated. Dr. Steinberg estimates that such a vaccine could prevent rheumatoid arthritis in millions of people. ■

Of Mice and Men: The Path to Studying Disease

Linda Stalvey

The scientists in the Arthritis and Rheumatism Branch, NIADDK, have devoted their scientific careers to expanding the body of knowledge needed to treat, and perhaps some day to cure arthritis, a disease as old as man himself.

Studies currently in progress range from those at the molecular level through animal models, to clinical programs for patients with rheumatoid arthritis, systemic lupus erythematosus (SLE), and related diseases.

The clinical expression of rheumatic diseases includes inflammation which can be initiated by immune complexes—combinations of foreign substances (antigens) and proteins which the body makes to help remove foreign substances (antibodies). These immune complexes are part of the body's defense against infection. Also included in this defense are the white blood cells. It is important to understand what factors might turn this normal defense system into a cause of disease.

White blood cells or leukocytes produce antibodies that may be partially responsible for the joint inflammation and pain suffered by arthritis patients. In apheresis, the patient's blood is filtered into a machine which then spins the blood components into bands: the heavy red cells first, then the white cells, platelets, and finally the plasma. When the white cell layer is removed and discarded (the others are returned to the patient), the process is called leukopheresis. A doctor and technician usually monitor the process.

NIH PHOTO 1831

A Two-Pronged Approach to Investigation

Dr. Ronald Wilder, senior investigator in the Arthritis and Rheumatism Branch, studies inflammation using a two-pronged approach. First he studies the development of inflammation in rats, and then he studies patients who already have inflammation.

Rats injected with a bacterial cell wall (BCW) preparation made from Group A *streptococcus* (the bacteria that cause strep throat) will develop arthritis, with all the classical symptoms including inflammation, rheumatoid factor production and hypergammaglobulinemia. Different strains of rats react differently to the injection, some developing severe arthritis, some moderate arthritis, and some no arthritis at all. This observation led Wilder to believe that there was a genetic component involved in the susceptibility to the disease of certain strains of rats. Because of variations within strains, it also appeared that several factors, rather than a single factor, were controlling the arthritis.

Further experimentation showed that in the resistant strains of rats the BCW preparation stayed in the spleen, near the site of injection. In rats that developed arthritis, the preparation migrated to the joints before becoming stationary.

Under normal conditions the researchers would expect the white blood cells to phagocytize or eat the "foreign" bacterial preparation. Since this apparently does not happen in arthritic rats, it appears that there is a defect in this part of the defense mechanism. This finding needs further definition.

Lymphocytes and macrophages are types of white blood cells that play major roles in the inflammatory process. Often the question is asked whether joint inflammation in patients would be reduced if these cells were removed.

In clinical trials, patients with severe rheumatoid arthritis were treated with leukapheresis, a process that removes white blood cells. In certain patients inflammation was reduced. Those who responded usually did so within the first week of therapy. There was no correlation between inflammation and the number of cells removed, or the number of times the patient was "pheresed."

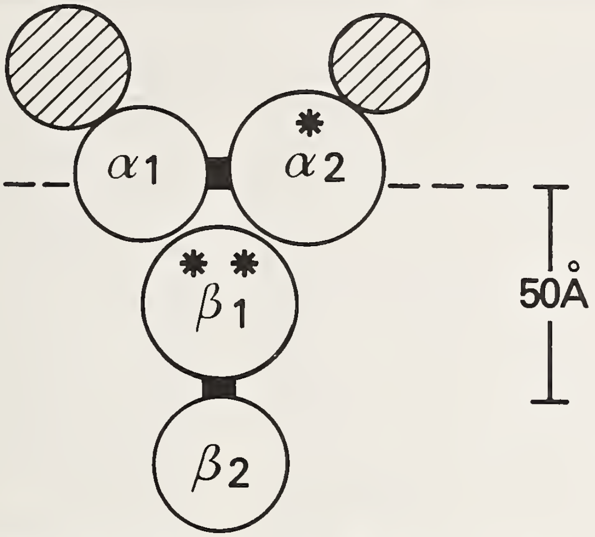
However, there appeared to be a correlation between improvement and the type of cell removed in pheresis. When abnormally-functioning cells, cells which are "activated," were removed, the patients improved. While results of this and other studies on pheresis are promising, a great deal of additional study is needed before the process is completely understood and evaluated as a treatment tool.

Antigens, Antibodies, Inflammation and Basic Research

Dr. Paul Plotz and colleagues, in the Arthritis and Rheumatism Branch, are examining the antigen-antibody portion of the inflammation process. They have developed a family of test antigens for making model antigen-antibody complexes. With these complexes, they have shown that the chemical structure of the antigen can attract the antigen-antibody complex to abnormal sites instead of to the sites to which they normally go for disposal.

The major implication of the experiments is that the structure of the antigen can influence where the antigen-antibody complex goes and might therefore be responsible for the apparent failure of the normal defense mechanism, which allows complexes to set up inflammation at abnormal sites.

Structural studies of antigens, while providing important information, are, in a sense, only half the story. Dr. Henry Metzger's group is studying the nature and effect of antibodies. Their work is related to inflammation, and also h broad applicability in biology, specifica in understanding the immune system.



A schematic model (proposed by Henry Metzger and his colleagues) of the receptor on cells which binds IgE antibodies. The "alpha" subunit composed of protein and carbohydrate (shaded circles) binds IgE. The newly discovered "beta" subunit may anchor the "alpha" chain to the membrane and may be involved in the mechanism by which the receptor causes the cell to release active chemicals.

NIH PHOTO 1832

The studies are focused on how antibody activates the release of inflammatory substances from cells. In reactions mediated by antigen-antibody complexes it is necessary for antibodies to aggregate or clump together for biological action. Usually the antibodies that clump together are attached to the cell surface by receptors. When an antigen attaches to the antibody on the cell surface, a chemical change occurs. This change is a message to the cell that an antigen is present. Dr. Metzger is attempting to describe the receptor for the IgE antibody by biochemical means. Once the structure and function of the receptor is known, it may give a clue to how the subsequent biological events can be identified.

Systemic Lupus Erythematosus

Both basic and clinical studies of lupus, (systemic lupus erythematosus or SLE) are also under way in the Arthritis and Rheumatism Branch. Animal models of lupus, such as New Zealand Black (NZB) mice, enable researchers to perform detailed studies of the cause and cure of the disease, not always possible with patients.

Much of the animal work has been performed by Dr. Alfred Steinberg and colleagues. They have characterized the effects of age, sex, immune stimulation, the thymus, and genetic factors in the expression of autoimmunity in NZB mice. Spontaneously occurring lupus in mice is characterized by distinct clinical syndromes with corresponding, but different, cellular and genetic bases. Patients with lupus also display varied clinical and serological symptoms. Steinberg thought human clinical syndromes could be similarly characterized.

Recent studies by the investigators suggest lupus is not a single disease entity, but an aggregate of clinical syndromes with different immunoregulatory abnormalities and associated symptoms. By characterizing ratios of specific white cell populations, T cells, suppressor cells, and helper cells, Steinberg has been able to divide the lupus symptoms into distinct clinical subsets.

Using monoclonal antibodies to derive the ratio (Rt) of helper cells to suppressor cells, (the most common immunoregulatory abnormality in lupus is a deficiency of suppressor cell activity), Dr. Steinberg discovered that Rt varied over a much broader range in lupus patients than in control groups. Lupus patients formed three groups: one with low, one with normal, and a third group with high Rt. Low Rt was observed in patients with severe renal disease, thrombocytopenia, and lupus onset at 20 years of age or less. Patients with high Rt had multisystem disease including lymphadenopathy, but only rarely lupus renal disease. Patients with normal Rt had the most widespread multisystem disease, often involving the kidneys and central nervous system.

This study suggests that genetic factors play an important role in the pathogenesis of lupus in humans. More direct approaches to the study of the pathogenesis of lupus, and ultimately, perhaps, to more individualized therapy may be possible with this knowledge.

The Chronicity Index—Important in Planning Therapy of Lupus Nephritis

Cytotoxic drug therapy is a controversial regimen used in trying to arrest end-stage renal disease in lupus patients. Dr. John Klippel has defined subsets of patients with lupus nephritis based on their Chronicity Index, with hope of better preserving kidney function in patients taking cytotoxic drugs.

The Chronicity Index is a semiquantitative histologic analysis of the type and degree of changes in kidney biopsies which has been used by Dr. James Balow, another senior investigator in the Branch, in studying patients with lupus nephritis. Using this scoring system, Dr. Balow discovered that substantial degrees of irreversible renal damage are often observed in patients who have normal kidney function tests, primarily serum creatinine.

Dr. Klippel's study showed that patients with a low Chronicity Index had a good renal outcome when treated with the cytotoxic drugs, azathioprine and cyclophosphamide, or prednisone.

Patients with a high Chronicity Index had poor renal outcome when treated with any of the drugs because of the presence of extensive and often irreversible kidney disease. This suggested that new therapeutic protocols should be developed for these patients.

Studies of patients with a moderate Chronicity Index showed responses to azathioprine and cyclophosphamide that appeared to be superior to prednisone, but this finding also needs further study in a larger clinical trial.

This study emphasizes that determining whether the patient has reversible or irreversible causes of impaired kidney function is important in planning therapy and in the overall prognosis of lupus nephritis.

Research in the field of arthritis and related disease is divided into two broad areas; the treatment of the symptoms of the disease and investigations into the cause or causes of the disease. Strides in treatment have been numerous; strides in revealing the cause(s) and cure are fewer, perhaps because these diseases are multifactorial, that is, several causes may contribute to their development.

Dr. John Decker, Chief of the Arthritis and Rheumatism Branch, feels that "Research has come about 75 percent of the way in the search for an arthritis cure." Perhaps when the question is asked again, in another ten years, an answer will be available. ■

Lupus: On the Edge of Discovery

Barbara Weldon

Systemic lupus erythematosus (lupus or SLE) is a potentially serious, complicated, inflammatory connective tissue disease that can affect many parts of the body, including the joints, skin and internal organs.

According to the Lupus Foundation of America, there are approximately 500,000 people in the United States who have the disease with more than 50,000 new cases diagnosed each year. Almost 90 percent of its victims are women of child-bearing age.

Twenty years ago lupus patients had a very high mortality rate but now—with better diagnosis, more effective drug treatment and medical management—the outlook for these patients is much brighter and many can look forward to living normal life spans.

NIADDK is supporting numerous diverse research projects on the cause and treatment of lupus. Studies on the disease include immunological abnormalities; genetic factors; complications in the kidney; central nervous system involvement; estrogen metabolism abnormalities; and improved therapies.

One NIADDK intramural study under the direction of Dr. Thomas A. Lehman is concerned with central nervous system (brain) involvement. The study is investigating the natural history of the neurologic disease of lupus in terms of clinical classification, onset, duration, recurrence, and presence of systemic features.

Another study is concerned with genetic factors. Dr. Lehman and his colleagues are investigating patients with lupus, their spouses, and immediate "blood relatives." Patients are questioned regarding drug intake, nature of household contacts, and signs or symptoms of lupus. Blood samples are then drawn from each family member for evaluation. The purpose of this study is to determine the significance of genetic factors and blood abnormalities found in immediate relatives of lupus patients.

Much of the current research on lupus focuses on the immune system and the role of antigens (substances that provoke the immune response) and antibodies (which are produced in response). Experimental animal models have been developed in inbred strains of New Zealand and other specially developed strains of mice. These studies have demonstrated that certain types of white blood cells that normally keep the antibody-producing cells in check are defective in lupus. Teams of investigators confirmed these observations and also found that decreases in the white cells were well correlated with disease activity. Replacement of deficient cell material may be a possible treatment for lupus in the future.

Dr. Peter Schur of Brigham and Women's Hospital, Boston, and other NIADDK grantees also have been investigating several immunologic tests that have been developed for lupus. They have found that abnormal levels of certain complement proteins and anti-DNA antibodies can predict when lupus may become active, and thus guide treatment of individual patients.

Grantee Dr. Norman Talal and his colleagues demonstrated that estrogens (female hormones) accelerate, and androgens (male hormones) suppress, lupus in mice. In addition, Drs. Robert Lahita and Henry G. Kunkel of the Rockefeller University in New York recently reported that women with the disease have an abnormality of estrogen metabolism. One hope for more effective treatment of lupus in the future may be to correct the sex hormone imbalance.

Dr. Charles Christian and his staff at the Hospital for Special Surgery in New York have found that methylprednisone (a cortisone-like drug) given in pulses of high doses intravenously to those with worsening kidney disease can improve kidney function, lessen clinical symptoms, and reduce the quantity of immune complexes in the circulation, with fewer side effects than when the drug is given at lower, more continuous doses orally.

An important complication of lupus during prednisone therapy is ischemic bone necrosis, in which poor oxygen supply to the bones can lead to bone deterioration. Drs. Thomas Zizic and Mary Betty Stevens of the NIADDK-supported

An excellent model of systemic lupus erythematosus exists in females of the New Zealand Black/New Zealand White hybrid mouse (shown in the left photo). Crossing a male New Zealand White and a female New Zealand Black mouse (shown in the right photo) produces a hybrid strain in which the females naturally develop lupus.

NIH PHOTO 1833

Multipurpose Arthritis Center at Johns Hopkins University, have identified factors that indicate which patients are at high risk for this problem. They have developed methods of early detection and treatment in order to prevent progressive damage to bone.

Several reports on lupus research projects were presented at the Eighth Pan-American Congress of Rheumatology held in Washington, D.C., last June. Dr. Eng Tan of the University of Colorado School of Medicine, and his committee reported on newly revised criteria for the classification of lupus. The study group analyzed 30 potential criteria (including all of the 1971 criteria) using the NIADDK-supported ARAMIS data bank for data storage and processing. The 1982 revised criteria require four or more of the following clinical features and/or laboratory abnormalities: (1) malar rash; (2) discoid lupus; (3) photosensitivity; (4) oral ulcers; (5) arthritis; (6) proteinuria greater than 0.5 grams per day; (7) seizures or psychosis; (8) pleuritis or pericarditis; (9) hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia; (10) antibody to DNA or antibody to Sm or LE cells or false-positive STS; and (11) positive fluorescence antinuclear antibody test. These criteria will help to standardize the definition of lupus as a baseline for clinical research on the disease.

At this meeting, Dr. Daniel Lopez-Acuna of Johns Hopkins University reported the nationwide mortality rates for the period 1968 to 1978 to assess patterns of age-, sex-, and race-specific death rates in lupus. Analysis of temporal trends revealed a significant overall decline in mortality rate. In addition, Dr. Lopez-Acuna confirmed a previously noted excess of lupus among non-whites. He also reported the high incidence of the disease in the Hispanic population in this country. His study demonstrated an increased mortality rate from lupus among the Puerto Rican population compared to other caucasians in New York City. He said that the predisposition of some ethnic groups to develop lupus may be a consequence of ethnic differences in the immune response.

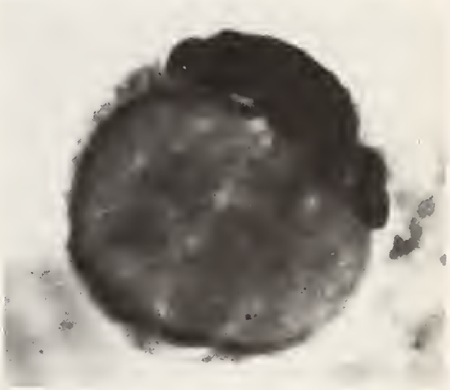
A comprehensive study of male patients with lupus was reported by Dr. Marion Miller of the University of Toronto. She studied 51 caucasian men with lupus and found no difference in the severity of the disease when compared with women lupus patients. The difference occurred when measurements of plasma estrogen and androgen hormone levels revealed at least one abnormal value in 15 of 17 males studied.

Dr. Peter Schur studied 42 caucasian families with at least one member having lupus to determine if there was an association between HLA genetic determinants and the presence of lupus. His studies showed a higher frequency of shared HLA determinants among parents in the study group than those found in the normal caucasian population. Offspring appeared to inherit the same genetic determinants. These studies provide evidence that HLA-linked genes may operate in a recessive manner genetically in the development of lupus.

Dr. Schur also evaluated a series of patients who had been followed since 1967 and who had gone into remission. He found that those who went into remission early in the course of their disease relapsed early. Those who went into remission later tended to stay in remission. If a patient stayed in remission longer than 18 months, she or he was likely to have a long remission.

Dr. Gino DiVittoria of the University of Alabama presented a study on pancreatitis in lupus, a previously unrecognized feature of the disease. According to Dr. DiVittoria, of 168 lupus patients admitted to the University of Alabama Hospital, seven cases of pancreatitis were identified. These patients had abdominal pain, fever and arthritis. Multisystem involvement including kidney disease and central nervous system involvement (CNS) was observed in each case. The study concluded that the diagnosis of pancreatitis should be considered in lupus patients with abdominal pain, particularly those with evidence of active multisystem disease.

Despite considerable research, the cause of lupus still remains a mystery. According to Dr. Lawrence E. Shulman, Director of the Division of Arthritis, Musculoskeletal and Skin Diseases, NIADDK, "It is gratifying to note that lupus research continues at a high level of activity, with promise of uncovering one or more major etiologic factors in the future." ■



An LE cell is seen under a microscope. Special blood tests, including the LE cell test, are used to detect the presence of lupus. Most patients with lupus will have a positive LE cell test reaction at some point in the disease.

NIH PHOTO 1834

Teamwork Pays Big Dividends in Multipurpose Arthritis Centers

Barbara Weldon

Proper exercise is very important since arthritic joints, if not used, tend to become stiff and permanently limited in motion. These arthritis patients are taking part in a pilot program developed by Stanford University which consists of 14 hours of self-management education within a three-month period. (Photo courtesy of the Stanford Multipurpose Arthritis Center.)

NIH PHOTO 1835

In the health research community, the word "center" may mean different things to different people. An Arthritis Center was defined by the 1976 Arthritis Plan "not as a structure of steel and concrete, but as a group of formally cooperating health personnel."

Through the support of NIADDK there are currently 20 Multipurpose Arthritis Centers (MACs) located throughout the country. The purpose of the "MACs" is to develop new knowledge and new methods for the application of existing knowledge for the ultimate benefit of patients with arthritis and related diseases.

These Centers conduct programs in three major areas: basic and clinical research; professional, patient and public education; and community demonstration projects and health services research. Some Centers may choose to develop special competence in one or more of the three components. For example, one Center might emphasize a particular type of arthritis, such as juvenile arthritis or osteoarthritis, or an aspect of bone or joint research such as biomechanics or bone metabolism. Another Center might focus its attention on a basic research area, such as immunogenetics, while still another Center might specialize in new techniques in professional, patient or public education or health services research.

Many of the research projects supported by Center funds are primarily developmental and feasibility studies. These studies complement ongoing research support in a given institution and are designed to encourage investigators to explore innovative scientific approaches, which may later form the basis of applications for investigator-initiated research awards from NIH or other agencies. The projects supported are diverse and include basic studies ranging from the role of cartilage proteoglycans in degenerative joint disease, to the possible viral etiology of arthritis, and the use of hybridoma technology to investigate anti-DNA antibodies in systemic lupus erythematosus, as well as clinical investigations.

For example, the MAC located at Brigham and Women's Hospital in Boston, directed by Dr. Matthew H. Liang, is investigating a new experimental approach in the treatment of severe rheumatoid arthritis. The researchers are studying total irradiation of the lymph nodes of patients who have been unresponsive to other forms of therapy. The rationale behind this procedure is based on previously observed immunosuppressive effects of radiation. In rheumatoid arthritis, the pain and inflammation may be the result of the immune or defense system reacting somehow against the body itself. The radiation treatments seem to produce a regression of the disease in patients with severe rheumatoid arthritis. In addition to the potential for treating difficult cases of rheumatoid arthritis, this study is yielding information on the role of lymphocytes in the development of the disease.

Similarly, the Stanford University Arthritis Center in California, directed by Dr. Halsted R. Holman, is studying total lymphoid irradiation as a potential therapy in patients who have another severe rheumatic disease, systemic lupus erythematosus.

At another Center, as part of a comprehensive study of the genetics of the rheumatic diseases, the Johns Hopkins University MAC in Baltimore, Maryland, is attempting to determine why two highly inbred populations (the old order Amish and the Mille Lacs Band of Chippawas) are more susceptible to psoriasis and psoriatic arthritis in the Amish and rheumatoid arthritis in the Chippawas.

According to Dr. Frank Arnett, principal investigator for the project, "the inbred (Amish) population will be compared with the outbred (normal) population for genetic markers predisposing them to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and other rheumatic diseases." The Amish are an especially appropriate group for studies of this nature for a number of reasons: they are a genetically closed population; the gene pool is relatively small; the average family

Researchers at the Boston University Arthritis Center are investigating the development of joint inflammation following infection by the bacteria gonoccocus. (Micrograph courtesy of Dr. Chalres C. Brinton, Jr.)

NIH PHOTO 1837

MAC community demonstration projects include studies of model health care delivery for the home-bound arthritis patients. (Photo courtesy of the Robert B. Brigham Multipurpose Arthritis Center.) **NIH PHOTO 1836**

is large; and extensive genealogical histories are available. The study will also investigate any environmental factors that may explain the increased frequency of the diseases in these populations.

Another study, at Boston University, is directed by Dr. Alan S. Cohen, an outstanding investigator in the field of amyloidosis (deposits of protein in the tissues). This Center is evaluating the soft tissue uptake of bone scanning radionuclides in patients with amyloidosis, in order to find a diagnostic test which would not require tissue biopsy.

Education is another important aspect of the Multipurpose Arthritis Centers. The Centers are expected to provide leadership in the formulation, initiation, development and coordination of education and training programs in arthritis for the full range of health professionals, including physicians in practice and in training, nurses and allied health professionals, and patients, their families and the public.

Dr. Kate Lorig of the Stanford University Arthritis Center has developed an innovative, comprehensive education program for arthritis patients, consisting of 14 hours of arthritis self-management education given over a three-month period to patients and interested family members. Statistics on the first group to complete the program showed a decrease in pain and an increase in normal physical activity. These improvements continued for almost two years after the program began. "We believe our study clearly demonstrates that health education works and changes people's lives," says Dr. Lorig. This new program is presently being adopted and evaluated on a national scale by the Arthritis Foundation.

Community demonstration and health services research projects are also a major feature of MACs.

In the field of health services research, the Center at Brigham and Women's Hospital is studying the cost effectiveness of joint replacement surgery in patients with arthritis pain and impairment. The objective of this study is to document changes in function and health status of patients after surgery, and to identify those individuals eligible for successful joint replacement. The investigators estimate that each year hip and knee replacement operations total 120,000 at an estimated annual cost of $840 million.

Community projects include studies of model health care delivery for the homebound arthritis patient, utilization of state and local agencies to conduct nursing and allied health professional education, and investigation of arthritis rehabilitation in industry.

In addition, many of the Centers have programs to deal with the problems of arthritis in children. At the University of Missouri Center in Columbia, directed by Drs. Gordon C. Sharp and Bernard Singsen, a comprehensive model care unit dealing with arthritis in children has been developed. This program includes a state-wide telephone consultation service, clinics, development of educational literature and the formation of a pediatric rehabilitation center. The model care unit has been integrated into the physicians' training program at the University medical school. As a result, medical students and residents in physical medicine, rehabilitation, child health, and rheumatology all spend a significant amount of time in the clinic as part of their training. The Center has also developed a series of lectures and conferences on juvenile arthritis for physicians specializing in family practice.

MACs have also developed core units or common-use facilities which increase the effectiveness and efficiency of each Center's activities. In biomedical research, there are core units for tissue culture, connective tissue metabolism, immunology, histocompatibility testing, and research involving hybridomas/monoclonal antibodies, to name a few. Core units in other areas are concerned with biostatistics, evaluation procedures, educational activities, and epidemiology.

The University of Alabama Center, directed by Dr. J. Claude Bennett, has developed a hybridoma core unit to enable investigators associated with the Center to use this new technology to produce highly specific antibodies as research tools. Core personnel are now able to: supply the necessary equipment for scientists who wish to produce their own hybridomas, but lack the facilities; assist in planning and performing immunizations and screening assays; and immunochemically analyze the antibodies that have been produced.

A related core has been established at Indiana University's Arthritis Center in Indianapolis. This core serves as a central facility for measurement of circulating immune complexes and *in vitro* antibody formation by human peripheral blood lymphocytes. It is used by Center staff in projects dealing with immune function in polymyositis, the role of complement in immune function, and the pathogenesis of hypogammaglobulinemia.

An evaluation core unit is in operation at the University of Michigan in Ann Arbor under the direction of Dr. Giles G. Bole. This core unit provides other centers with assistance related to all aspects of statistics, computer programming, questionnaire development, and data collection for on-going projects.

During the past several years, computers have been utilized in all phases of Center activities, including instruction, clinical research, and the use of the computer for patient management.

The Center at the University of Connecticut in Farmington, directed by Dr. Naomi F. Rothfield, has developed an effective and efficient way to enhance the education of physicians in various stages of training. At Farmington, a computer program that models rheumatoid arthritis has been developed. Information on a hypothetical patient, followed for a period of 17 years, was programmed into the computer. With this system, the intern, medical student, or post-graduate physician can sit at the computer terminal, access and recall the information, and be trained in diagnosis and treatment of the disease.

This program and other Center programs have been carefully developed to serve as models for other chronic diseases. The NIADDK program office for the Centers, led by Dr. Steven J. Hausman, carefully monitors the work of the various MACs through staff site visits, analysis of yearly progress reports, letters, phone calls, and a yearly meeting of the Center directors. In addition, NIADDK is currently developing methodology to evaluate the education and community components of the MACs. According to Dr. Hausman, "The cooperation of the individuals brought together in an Arthritis Center will ultimately lead to more rapid improvements in health care." ■

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National Institutes of Health
Building, 31, Rm. 2B-10
Bethesda, Maryland 20205

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NIH PHOTO 1838

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

News&Features
from NIH

March 1983

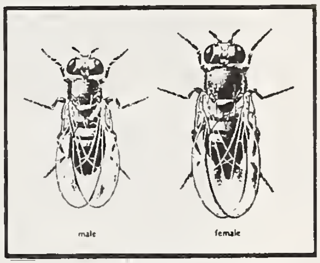
One of the most serious childhood diseases, measles, may soon be a thing of the past. In 1977, the Public Health Service instituted a program to ensure that 90 percent of the children in this country were vaccinated against measles and several other childhood diseases. As a result, the number of measles cases in the U.S. dropped to an all-time low in 1982. Challenges still remain, such as cases being brought in from abroad, numbers of young adults who are still unprotected, and infants who are too young to be vaccinated. But strategies of immunization, surveillance, and control of outbreaks are being used to try to bring about the complete eradication of measles in the near future. See page 2.

NIADDK has developed the first comprehensive informational booklet for patients on Paget's disease of bone.

The disease, which is characterized by excessive bone breakdown and formation of new bone that is dense and fragile, affects about three million Americans over age 40 and who are usually of western European heritage.

The cause of Paget's disease of bone is unknown, and the symptoms are often mistaken for those of rheumatoid arthritis.

Researchers have found that therapy with agents which block bone breakdown and formation has been successful in abating the progress of the disease. See page 5.



For the first time, a functional gene has successfully been transferred to a complex organism.

Researchers at the Carnegie Institution, under a grant from NIGMS, have devised a system to carry the gene that produces red eyes in fruit flies.

The next generation of fruit flies carried the red-eye gene in their germ lines, as evidenced by their production of offspring with this characteristic.

This success will greatly help in understanding how genes function in higher organisms. See page 7.

NINCDS grantees at the University of Pittsburgh have found that decongestants and antihistamines, popularly prescribed treatments for "secretory" otitis media, are ineffective.

The three-year study involved 611 infants and children with this middle ear inflammation who were divided into two groups. One group received an oral decongestant and an antihistamine, and the other group was given a placebo. Results after four weeks were almost identical for the two groups.

Otitis media is a common condition in preschool children, and although antibiotics or even surgery may sometimes be indicated in severe cases, it is often cured naturally without the need for any treatment. See page 6.

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Editorial Staff

Susan Gerhold
Acting Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

NIH News Branch
Building 31, Room 2B-10
Bethesda, Maryland 20205

Phone:
(301) 496-2535

Measles—A Memory?

Marian McGrath

Most of us remember having measles when we were children. Everybody got it; it was an inevitable part of growing up.

No longer. Thanks to development of an effective measles vaccine and rigorous immunization programs, fewer than 1,800 Americans were afflicted with this highly contagious viral disease in 1982, a 99 percent drop from the prevaccine era and an all-time low for measles in the United States.

Far from being an innocuous fact of life, measles (also called rubeola, hard measles, red measles and 7-, 9-, and 10-day measles) can be one of the most serious childhood diseases. The symptoms include fever and a generalized rash lasting at least three days, accompanied by cough, runny nose, or conjunctivitis (inflammation of the whites of the eyes and the lining of the eyelids). Recovery confers life-long immunity to subsequent attack.

The most common complications are middle ear infections (otitis media) in 9 percent of the cases and pneumonia in 6 percent. One measles patient in 1000 will develop encephalitis, a brain infection that kills 15 percent of its victims and leaves another 25 percent permanently brain damaged, with possible mental retardation, seizures, and deafness.

The risk of death from measles has declined over the years; nevertheless, about one death occurs among every 3,000 cases. Adults and infants have a higher risk of death from measles than do children and adolescents. Most measles-related deaths are caused by encephalitis or viral or bacterial pneumonia.

A late complication of measles, occurring an average of seven years later, is subacute sclerosing panencephalitis (SSPE). Apparently due to a "slow virus" infection, SSPE begins with mental deterioration and muscle spasms and progresses over months or years to generalized convulsions, coma, and death.

Measles has had a severe impact on American children since colonial times. Outbreaks were reported as early as 1635, and a major epidemic occured in 1713-1715.

The effect of measles on military personnel has been particularly brutal. During the Civil War, the disease struck more than 67,000 Union soldiers, claiming some 4,000 lives. Among World War I U.S. Army personnel, it was the fourth leading cause of death, after flu, pneumonia, and battle and nonbattle injuries, and ravaged the civilian population as well.

Measles epidemics swept the country every two or three years, with small localized outbreaks in the intervening years. The disease displayed a predictable seasonality, always peaking in mid-May and plummeting in early September.

Most children experienced the unpleasant symptoms of measles before vaccine was available. Complications sometimes caused death or permanent disability. NIH PHOTO 1839

Enforcement of laws requiring measles vaccination before entering or attending school has brought the incidence of measles to record low levels in the United States.

NIH PHOTO 1840

Between 1950 and 1962, the Centers for Disease Control (CDC) in Atlanta, Georgia, recorded about 500,000 cases of measles annually; approximately 500 of these victims died. However, CDC estimates that only one case in ten was reported, so that the actual incidence of measles was probably an awesome five million cases per year. About 90 percent of the cases occurred in children less than 10 years old, and 95 percent of all children had been infected by the time they were 15 years old.

The licensure of measles vaccine in 1963 led to a precipitous drop in the overall incidence of the disease as well measles encephalitis, deaths due to measles, and, seven years later, SSPE. However, each time federal support for measles immunization programs decreased, the disease rebounded. In addition, it became obvious that the mere existence of a vaccine, even when federal money was available to make it widely available, would not eliminate the disease.

Therefore, the then Department of Health, Education, and Welfare began an all-out attack, called the Childhood Immunization Initiative, in 1977. It had two goals: (1) to ensure that 90 percent of U.S. children were vaccinated against measles, mumps, rubella, polio, diphtheria, tetanus, and pertussis by October 1979 and (2) to develop a plan to maintain this level of protection permanently.

The immunization records of 28 million schoolchildren were reviewed. Children lacking evidence of immunity, through vaccination or by having had measles itself, were referred for vaccination. Existing requirements for vaccination as a condition of entering or attending school were enforced, and new laws were passed, By July 1979, all 50 states and the District of Columbia had such laws.

As a result of this effort, measles again began to decline. In fact, the progress was so encouraging that in October 1978 a new goal was announced: elimination of indigenous measles from the United States by October 1, 1982. (Indigenous cases are those that cannot be traced to a foreign source within two generations of transmission.)

Although the target date of October 1, 1982, has passed and measles is still with us, present trends indicate that the goal of making indigenous measles a memory may be achieved very soon. Since 1980, 96 percent of children entering school for the first time have been immunized. In 1982, 94 percent of the nation's 3,138 counties reported no measles cases, and there were no measles deaths anywhere in the country. For the first time in U.S. history, a measles-free week (January 9-15, 1983) was reported.

In spite of these milestones, challenges still remain. Probably the toughest problem is eliminating measles imported from foreign countries, which accounted for about 36 percent of all U.S. cases in 1982. More than one-third of the imported cases came from England, Mexico, and India via unimmunized foreign citizens or traveling Americans, with 29 other countries also identified as origins. Since measles occurs worldwide and measles immunity is not a requirement for entry into the United States, the cooperation of foreign public health agencies is necessary if nonindigenous measles is to be eradicated. Americans can protect themselves by making sure they are immunized before traveling abroad.

A second challenge is to identify unprotected adolescents and young adults. Recent measles outbreaks in junior and senior high school, colleges, and military bases have indicated that these populations lack proper immunity, probably for one of two reasons: (1) The widespread use of measles vaccine has reduced the incidence of disease among preschoolers and young schoolchildren so that susceptible children reach an older age before exposure; (2) some of the early vaccination practices are now considered less effective, specifically, the use of inactivated vaccine and vaccination of children less than 12 months old.

In the past few years, several measles outbreaks in day-care centers have highlighted a third problem population: children who are too young to be immunized. Although the recommended age for vaccination is 15 months, children who are likely to be exposed, such as those in day-care centers, should be immunized at 6 months, and again at 15 months. Most newborn infants are protected for the first few months by transplacental antibodies if their mothers have measles immunity. Because the risk of serious complications from measles is high in very young children, immunological protection is vital.

What can be done to meet these challenges? The plan is a three-pronged attack of immunization, surveillance, and control of outbreaks.

Immunization is the most important element of the plan. A high level of immunity has been attained in the population because of existing school immunization

NIH PHOTO 1841

NIH PHOTO 1842

NIH PHOTO 1843

Measles is a universal disease that has been recognized for at least 1,900 years. These early 20th century Japanese woodblock prints show (1) a warrior armed to keep measles away, (2) the use of barley, black beans, and liquid to cure measles, and (3) a violent public fighting the demon measles. (Photos from National Library of Medicine)

Lithograph in Scottish physician Byron Bramwell's *Atlas of Clinical Medicine*, published in 1896, shows the typical measles rash. The text claimed that measles was due to a "particulate, organic, living poison." (Photo from National Library of Medicine) NIH PHOTO 1844

laws. Public health experts emphasize that vigorous enforcement of these laws must continue.

To ensure effective surveillance, physicians must report measles cases to health departments, and public health workers must continue to routinely seek out any unreported measles cases in day-care centers, schools, and health-care facilities. This would guarantee that virtually all measles cases are tabulated.

Controlling outbreaks of measles requires the rapid investigation of suspected measles cases to confirm the diagnosis and pinpoint the source of the infection. Susceptible contacts of the measles patient are then either vaccinated or excluded from school until the risk of infection is over.

There is no doubt that vaccines have been the big guns in the war against measles. The first two vaccines were licensed in 1963: a killed one and a live, attenuated one. An improved live vaccine was licensed in 1965 and is the only one now available in the United States. It can be given alone but is usually combined with rubella and mumps vaccine.

Vaccination is routinely done at 15 months of age for maximum effectiveness. Children vaccinated earlier than 12 months of age should be revaccinated as should anyone who received killed vaccine. Unimmunized people exposed to measles should be vaccinated immediately, since data suggest that vaccination within 72 hours of exposure may protect against the disease.

Some people should not be vaccinated. These include pregnant women, because of the potential risk of infecting the fetus, and people who have a fever-producing illness other than a cold. In this case vaccination should wait until after recovery. Because the vaccine virus is grown in chick embryo cells, people with life-threatening allergy to eggs should also avoid vaccination. Others who should n be vaccinated are patients with leukem lymphoma, generalized cancer, or immune-deficiency diseases and those who are receiving certain drugs or radiation therapy.

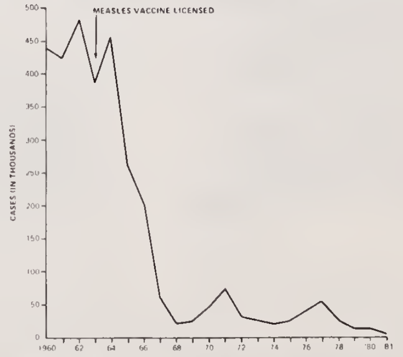
The measles vaccine is highly effective, producing antibodies in at least 95 percent of those vaccinated. Protection appears to be long-lasting and no booster is needed.

The 131 million doses of live vaccine administered through 1981 have had an excellent safety record. Side effects include fever in 5-15 percent of the vaccinees and a transient rash in 5 percent.

The effectiveness of an immunization program was demonstrated in the military. In 1980 the armed forces established a routine program for vaccinating all recruits, military school students, and day-care children and personnel. Only one case of measles in 1981 was traceable to the military, showing that the armed forces have apparently eliminated measles ahead of the nation as a whole.

The benefits of our 20 years of vaccine use are striking. CDC officials estimate that 48 million cases of measles have been averted, 4,800 measles deaths avoided, and 16,000 cases of mental retardation prevented. Approximately 1.4 million years of normal and productive life h been preserved by preventing death a mental retardation from measles. Nearly 160 million school days, 25 million physician visits, and 3 million hospital days have been saved. Every dollar spent for measles prevention has resulted in ten dollars in benefits, a net savings of $4.4 billion.

These benefits will continue to accrue as long as measles remains a memory. As observed by former Health and Human Services Secretary Richard Schweiker, measles lies "waiting for the unprotected—and only a continued aggressive program will keep up our defenses. Immunization maintenance must be a cornerstone of our health plans for the future." ■



The number of measles cases declined abruptly after the vaccine became available but rose again in 1971 and 1977 with decreased federal support for immunization programs. (Source: CDC) NIH PHOTO 1845

NIH Issues Pamphlet on Paget's Disease of Bone, Illness Which Affects Three Million Americans Over the Age of 40

Connie Raab

The first comprehensive patient brochure on Paget's disease of bone, an ailment which affects as many as three million Americans over age 40, has been issued by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK).

Understanding Paget's Disease was written and developed by NIADDK with the cooperation of the medical advisory board and Executive Director of the Paget's Disease Foundation, a national voluntary organization. "We welcome the appearance of this new, authoritative pamphlet on Paget's disease because it outlines the latest accepted methods of diagnosing and treating the disease," said John Johnson, Chairman and President of the Foundation. Copies are available from the Paget's Disease Foundation, Box 2772, Brooklyn, New York 11202.

Paget's disease of bone, technically known as "osteitis deformans," is a chronic disease of the skeleton with abnormally rapid bone turn-over. Excessive bone breakdown and formation can [illegible]sult in bone that is both dense and fragile, frequently occuring in the spine, skull, pelvis, thighs, and lower legs.

This complex disorder, whose cause is unknown and whose symptoms often are mistaken for the discomfort of rheumatoid arthritis, seems to afflict people of western European heritage most frequently. It is the subject of intensified study by scientists in many universities and therapies have been developed.

Paget's disease of bone was named for Sir James Paget who first described it in 1876. These drawings were done by Sir Paget [illegible] show bowing of the limbs, one character[illegible]ic of the disease. Paget's disease most commonly afflicts the bones of the spine, skull, pelvis, thighs and lower legs. (Drawings courtesy of the Paget's Disease Foundation.)

NIH PHOTO 1846

The actual prevalence of the disease may be more than has been reported because frequently Paget's disease patients have no symptoms and do not require treatment. There is a possibility it may be transmitted genetically since it often can occur in more than one member of a family. In most cases, however, it appears to arise spontaneously.

It should not be confused with "juvenile Paget's disease," a rare hereditary disease of children nor with Paget's disease of the breast to which it is unrelated.

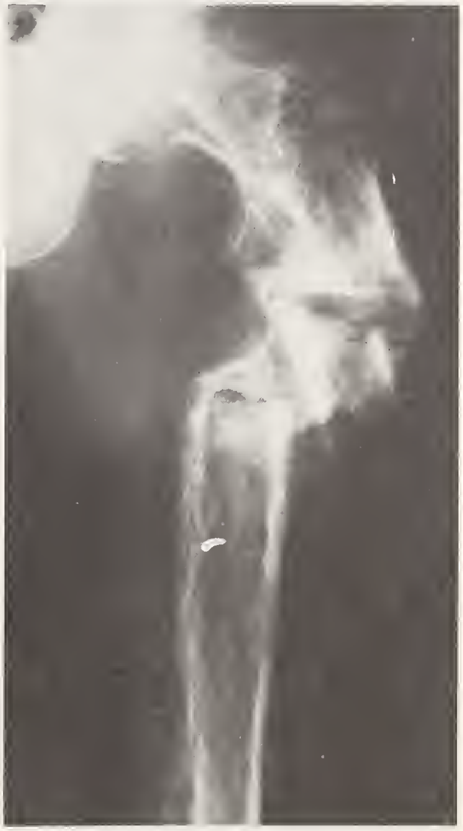
What happens in Paget's disease of bone is that the rate of bone turnover far exceeds the normal rate of action and some unidentified factor stimulates excessive bone breakdown. New bone forms in a disorderly way and the affected bones may become thickened and weak. In the initial stage of the disease, fat in bone marrow cavities is replaced to a large extent by blood vessels. The involved areas can cause pain, become deformed, and occasionally may fracture spontaneously.

During the active stage of the disease, abnormal bone turnover can continue for more than 20 years. Often an inactive stage will follow with normal bone cavity action. Far more common, however, is a course of slow continued progression.

Many patients are symptom-free but those who do have symptoms report pain, a sensation of heat, headaches, bowing of a limb or enlargement of the skull, muscle and sensory disturbances, congestive heart failure when the heart is overworked and pumps more blood through the thickened mass of blood vessels in active pagetic bone, hearing loss, or in extremely rare cases, osteogenic sarcoma, a form of bone cancer.

Tests for diagnosis include laboratory studies of blood and urine, most commonly measuring the level of the blood enzyme alkaline phosphatase, a by-product of bone-forming cell activity. X-rays, bone scans and biopsy may also be used to detect the disease.

Treatment slows the disease but does not cure it. Early recognition and treatment can bring about a good response in most cases. Treatment is often effective with calcitonin, a hormone produced by the thyroid gland, and the diphosphonate disodium etidronate. These agents work to block bone breakdown and formation and in many patients improve symptoms for a period of time. Mythramycin, a cytotoxic (cell-destroying) agent, has also been used to treat Paget's patients, and other diphosphonates are being developed.



In Paget's disease, excessive bone breakdown and reconstruction can result in bone tissue that is dense but fragile. As the disease advances the patient may develop bowing of limbs, arthritis (joint inflammation), a tendency toward fractures, nerve compression, severe aching and other symptoms.

This x-ray shows multiple thighbone fractures in the leg of a Paget's patient. (X-ray courtesy of the Paget's Disease Foundation.)

NIH PHOTO 1847

Although the cause of Paget's disease is not known, one theory is that it is the result of a slow-acting virus.

Investigators supported by NIADDK are pursuing research investigations at the University of Southern California, Massachusetts General Hospital in Boston, the University of California, San Diego, and in other university and research centers. ■

Popular Drug Treatment Prescribed for Otitis Media Proven Ineffective

Diane Striar

Decongestant and antihistamine compounds, one of the most popular drug treatments prescribed for a common childhood ear disease called otitis media with effusion (commonly known as "secretory" otitis media) are no more effective than a placebo, according to a study conducted by Dr. Charles D. Bluestone and associates at the University of Pittsburgh.

Also, the drugs cause significantly more side effects than does a placebo—primarily mild sedation and weakness.

Decongestant and antihistamine compounds "should not be recommended for otitis media with effusion in infants and children," concludes Dr. Bluestone.

This research was carried out under a contract with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

The 3-year study evaluated a combination of an oral decongestant (pseudoephedrine hydrochloride) and antihistamine (chlorpheniramine maleate). These drugs, either separately or in combination, are widely prescribed, as well as being available without prescription in drugstores.

Of 611 infants and children entered in the study, 553 completed a 4-week course of either decongestant-antihistamine therapy or a placebo that had no therapeutic value. The patients ranged in age from 7 months to 12 years. They were reexamined at 2 and 4 weeks for evidence of middle ear fluid. Patients who had no middle ear fluid at the end of 4 weeks were examined monthly for 3 more months to determine the rate of recurrence.

Diagnosis was made by examining the middle ear for inflammation, measuring middle ear pressure and hearing, and testing the middle ear muscle reflex.

This was a double-blind study. Neither the doctors nor their patients knew which children were taking the drug and which were taking the placebo.

Of the 278 patients who took the drug, only 69—about 25 percent—had no otitis media in either ear after 4 weeks of treatment. The 275 children who received the placebo had nearly identical results, 67—or about 24 percent—with no otitis media in either ear.

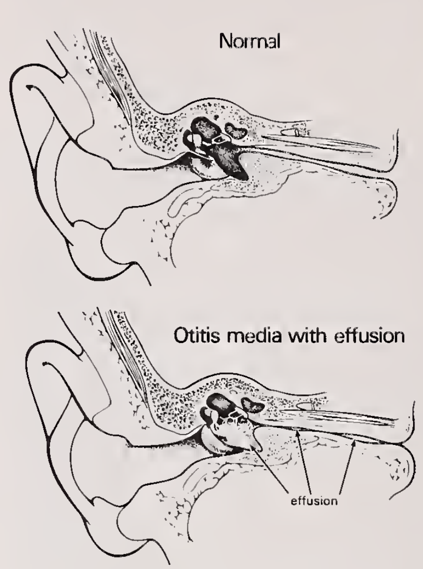
Neither the age of the children nor the length of time they had otitis media affected the results of the trial.

Dr. Bluestone's research team found no significant difference in hearing between the two groups of children. However, over 50 percent of the ears with otitis media still had a significant hearing loss after 4 weeks.

If these hearing findings are projected to the general population of children who have otitis media with effusion, report Dr. Bluestone and associates, "the seriousness of the disease becomes manifest. Large numbers of children may have significant hearing loss for extended periods of time during the most important period of language and linguisitic development."

An estimated two-thirds of preschoolers have at least one episode of otitis media.

Dr. Bluestone examines a youngster who has otitis media. NIH PHOTO 1848



NIH PHOTO 1849

For parents who are concerned about curing their children's ear disease, Dr. Bluestone points out that several alternative forms of treatment for otitis media are still considered effective, including antibiotics and surgical procedures.

"But," says Dr. Bluestone, "parents should also recognize that the disease has a natural cure rate on its own—without any surgical treatment or medication."

Dr. Bluestone cautions that these study results pertain to infants and children only. "We cannot draw the same conclusions about adults, who have a more efficient eustachian tube than children," he says.

In addition to differences in eustachian tube structure and function, children are more susceptible to otitis media than adults because they are more prone to colds or respiratory infections. Otitis media results when infected nasal secretions enter the middle ear, causing swelling, inflammation, and pain.

Decongestant-antihistamine medications are currently prescribed for otitis media because physicians believe they help to clear the eustachian tube of secretions.

Although the study found them ineffective for this purpose, Dr. Bluestone says people "should not throw these drugs away completely."

"They may be beneficial for other middle ear problems such as eustachian tube dysfunction without fluid," he suggests. The drugs may also be helpful in decongesting the nasal passages.

The study was conducted in cooperation with the Otitis Media Research Center, Children's Hospital of Pittsburgh. Dr. Bluestone is the Director of the Center, which is funded by a research grant from NINCDS. ■

Fruit Flies' Eyes Reveal Success of New Gene Transfer System

Doris Parker

One of the most exciting new developments in biology is the recent production of red-eyed fruit flies in a Baltimore laboratory. Not, of course, because the world needs prettier fruit flies, but because the red-eyes prove the success of one of the first systems scientists have devised to transfer a functional gene to a complex organism.

Red eyes are normal for wild fruit flies but some mutant strains of laboratory-bred flies have brown eyes. Now scientists have successfully transferred a red-eye gene into the cells of these laboratory insects.

Drs. Gerald M. Rubin and Allan C. Spradling of the Carnegie Institution of Washington, grantees of the National Institute of General Medical Sciences (NIGMS), have found a way to use moveable pieces of genetic material, called transposable elements, to carry a gene for red eyes into fly embryos which then develop and pass the gene on to their offspring. In doing so, the researchers have devised a powerful tool that will greatly aid other scientists working to understand how genes function and are regulated during development.

Although transposable elements were first inferred by classical studies of corn genetics 30 years ago, such elements are just now beginning to be more fully understood. Only recently have techniques been developed to provide physical evidence that transposable elements are actually discrete segments of DNA which can move from one location to another on a chromosome and even hop between chromosomes.

NIH PHOTO 1850

So far, transposable elements have been found in many organisms, including *Drosophila melanogaster*, a common fruit fly. Much is already known about *Drosophila* genetics: the insect has been a favorite model for genetic research for over 60 years.

The red-eyed fruit flies came about through collaboration between the two Carnegie scientists, who were working on complementary problems. Dr. Rubin had isolated and was studying various transposable elements called P elements. Dr. Spradling was studying the genetics controls on fly development and wanted to observe the effects of modified genes inserted into developing flies. He needed a suitable vector to ferry these genes into the DNA of fly reproductive cells.

Dr. Rubin managed to isolate a P element which seemed large enough to function independently as a transposable element. He used recombinant DNA techniques to produce sufficient quantities for the research.

Before they could use the element as a vector, the researchers needed to know if it could be successfully introduced and incorporated into the fly embryo DNA. To prove that the element got into the DNA, they wanted a genetic marker—preferably a visible marker that wouldn't require a complicated biochemical test to determine its presence.

For several years P elements have been thought to be a primary cause of a relatively common group of fruit fly mutations which induce a syndrome known as hybrid dysgenesis. One of these mutations, which involves the shape of the bristles found on the fly thorax (midsection), was an ideal marker since it could easily be seen.

Embryos from flies with normal bristles, which were known not to be carrying P elements, would be injected with the cloned P element carrying the bristle marker. Once they matured, the injected flies would then be mated to flies which had no P elements. Offspring with mutated bristles would show that the P elements had successfully entered the fly germ line (cells responsible for reproduction). The experiment was a long shot, since it was by no means certain that the particular P element the researchers injected was sufficient to produce the change.

Drosophila melangaster embryos are extremely tiny and fragile; the process of microinjection kills most of them. Fortunately, some embryos survived this experiment, matured, and were mated. In two weeks, when they could examine the mature offspring, the investigators were delighted to see that a number of the flies showed significant bristle mutation. The cloned P elements had incorporated into the embryo DNA.

Drs. Allan C. Spradling (left) and Gerald M. Rubin sketch a diagram of their gene transfer system which uses a transposable element as a vehicle for carrying the gene for red eye color into brown-eyed fly embryos.

NIH PHOTO 1851

The next series of experiments was set up to test the usefulness of the P element as a vector. The researchers used recombinant DNA technology to attach a cloned gene for red eyes to the P element. They then injected the hybrid element into brown-eyed fly embryos.

Again the experiment was a success. Between 20 and 50 percent of the next generation of flies carried the red-eye gene in their germ lines, as indicated by their ability to produce offspring with red eyes.

News of success travels fast, especially in such a rapidly developing field as genetics. Already other biologists are beating a path to the Carnegie lab—Dr. Rubin reports they have sent clones of the P element to over 100 laboratories. Some of these investigators will test the ability of such elements to function in other organisms.

Using P elements to transfer genes has many advantages over other methods, such as those using viral vectors. These elements are more efficient, since they insert into the recipient DNA, apparently without becoming rearranged—and inactivated—in the process. In addition, a relatively large gene can be transferred by this method—the red-eye gene, for instance, is three times the size of the P element itself. Finally, in contrast to other systems, the inserted genes can be stably transferred from generation to generation.

Although transposable elements have not yet been isolated from most higher organisms, including humans, it may be that all species will prove to have them. It may someday be possible to use transposable elements (though not necessarily P elements) to help induce beneficial changes in plants and animals. For the present, Drs. Rubin and Spradling have provided their fellow scientists with a very valuable tool which should stimulate important new research and advance our understanding of how genes control functions in higher organisms.

In recognition of this achievement, Drs. Spradling and Rubin were recently selected to receive the 1983 Young Scientists Award of the Passano Foundation. ■

Gene Mapping: Key to Conquering Neurogenetic Disorders

Elizabeth Pennisi

Dystonia, neurofibromatosis, muscular dystrophy, Tay-Sachs disease, Huntington's disease—the list of neurological disorders caused by faulty genes seems endless. Many others, including some forms of epilepsy, Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis, may also be influenced by genetic predispositions.

These illnesses affect the nervous system and all, at least in part, result from miscoding of information in the genes, the information carriers that are passed from parent to offspring. The dual genetic and neurological nature of these diseases has shaped current approaches to their treatment, care, and prevention.

As head of clinical neurogenetic studies in the Neuroepidemiology Section of the National Institute of Neurological and Communicative Disorders and Stroke's (NINCDS's) Intramural Research Program, Dr. Roswell Eldridge investigates some of the more than 500 neurogenetic disorders. In his research he combines genetic study of families and twins with epidemiology, the investigation of a particular disorder in large populations, to understand how heredity and environment interact to cause disease.

His goals are to determine the specific causes for neurogenetic illnesses, to evaluate treatment, and to develop guidelines for parents about the risks of passing these diseases on to their unborn children. The ultimate aim is to prevent these crippling, and sometimes fatal, diseases.

Neurogenetic disease can be defined as any inheritable trait that interferes with nervous system function. There are some that are very well known: the muscular dystrophies, neurofibromatosis, and the various movement disorders like Huntington's disease or the torsion dystonias. But there are more than 500 of these so-called "single gene" disorders that now are recognized, in which it is suspected that a mutation in a single gene produces the disease, for instance, in Tay-Sachs disease.

Other neurologic disorders are not due to single gene changes. Instead there seems to be an interaction between genetic and environmental factors. These are "multifactorial" diseases. Multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's disease may be examples. In these disorders no single gene or single event, such as an infection with a virus, is responsible. Rather, there is an interplay of several factors. There is a tendency for multifactorial disorders to run in families, but they do not show classic inheritance patterns like the single gene disorders.

Single gene disorders are relatively simple to diagnose if there is an accurate biochemical test, as in Tay-Sachs, or if there is a long family history of, for example, Huntington's disease, and the individual developes the characteristics of that condition.

But if there is no diagnostic test or family history, and only mild signs are present, the diagnosis could be very difficult. Often a period of observation is necessary. Patients are sometimes asked to keep diaries about their particular problems, what might precipitate symptoms, and what might help control the disorder. A detailed family history is very important and sometimes relatives' medical records are studied also.

Types of treatment vary. In Wilson's disease, a rare disorder associated with abnormal movements and liver disease, copper metabolism is abnormal. Copper accumulates in certain parts of the brain and leads to many of the symptoms. A drug that helps remove the excess copper and thereby correct symptoms, or at least prevents their progression, can be administered. But unfortunately, most disorders—Huntington's disease and the muscular dystrophies, for example—cannot yet be cured. Haloperidol is used to treat Tourette syndrome, but with many of these chronic disorders there are no specific drugs. One problem in dealing with patients and families is that as soon as there is any mention of a possible drug or therapy, regardless of how preliminary the observations are, there is of course tremendous interest generated. Unfortunately, there can also be a lot of disappointment.

Dr. Eldridge believes it is very important with these chronic conditions that there be the test of time—many months or years spent observing the effects of the particular drug or therapy on the condition in a large number of individuals before a conclusion is reached regarding a new drug or therapy's effectiveness. He feels that it is possible to find cures for all neurogenetic disorders. Once a diagnosis of genetic disease is made, we then know the basis of the disease. In the case of a single gene disorder, there is a mutation in the genetic material and the gene results in a specific chemical abnormality in the body. It is a matter of identifying the gene's abnormal product and then finding a means of correcting the effect of that product. That has been done now for a number of conditions and potentially is possible for all genetic disorders. Dr. Eldridge says that once we know that we or our family has the disease-causing factor—the mutant gene—we could choose to limit the size of our family or to monitor pregnancies to increase the likelihood of having healthier children.

Research approaches for single gene disorders differ from approaches to multifactorial diseases in that if a single gene disorder is suspected close blood relatives of patients are studied to look for

Dr. Roswell Eldridge of NINCDS explains to a patient how genes carry information from parent to offspring.

NIH PHOTO 1852

specific inheritance patterns. The intention is to try to locate a single faulty gene product, such as a protein or enzyme that does not function correctly.

In contrast, in multifactorial diseases unrelated populations can be studied a well as families. Currently, research is being conducted on twin pairs with Alzheimer's disease.

A new approach in research concerns genetic linkage, knowing what genes are located close to each other on the chromosome. Genes are lined up on the 46 chromosomes. Researchers are trying to find at what point on a particular chromosome a mutant gene lies and what well-documented genes lie close by. Then it can be predicted who in an at-risk family will carry the mutant gene by looking at what other genes are carried. For example, if a mutant gene lies next to the genes for ABO blood type, which blood type in that family is linked with the disease can be determined and then used to identify, even before any disease symptoms appear, who in the family might develop the disease and pass it on. This information is already used for counseling.

Dr. Eldridge likens gene mapping or linkage to that of mapping the world. "Now we have very precise methods for mapping any particular area of the world. We can define where Bethesda, Md., is very accurately. We can do this from satellites thousands of miles above us with estraordinarily precise techniques. We are seeing parallel developments in gene mapping that are going to permit us to pinpoint each gene and know how all the genes are related to each other on the chromosome. This coupled with the increasing understanding of the mechanism by which genes act is going to revolutionize our approach to people with genetic disorders. We will be able to tell whether a given gene is abnormal or not. Through advances in gene biology we will know how to apply this information to correcting or preventing single gene disorders."

He does not think opportunities in the multifactorial disorders will be as dramatic, but as we learn about risk factors that might lead to these conditions, we can consider ways to avoid them in individuals who are genetically suspectible.

According to Dr. Eldridge, right now we know where the faulty gene lies on the chromosome in less than 30 of these single gene disorders. And in some of the major disorders, like Huntington's and neurofibromatosis, we do not even know how the faulty gene upsets the body's chemistry to cause the disease.

Dr. Eldridge emphasizes that there is a great need for the neurological community to prepare to handle the coming tidal wave of information that advances in gene mapping will bring, and the implications of this information for the hundreds of thousands of affected patients and their families. ■

Programmed for Success: A Computer Helps Us to Help Ourselves

Sandra D. Levine

Computers have been firmly establishing their place in medicine for some time, but it seems they may also serve as useful tools to improve people's health-related behavior.

From the Veterans Administration Hospital in Montrose, New York, comes one example of this type of behavior modification—using a computer to help people stop smoking.

This new technique was described by D. Sid J. Schneider, a research psychologist at the Montrose V.A. Hospital, at a seminar presented at NIH in January.

Statistics apparently indicate that 90 percent of smokers wish they did not smoke, but only 20 percent would be willing to attend formal stop-smoking programs. Therefore, Dr. Schneider divised a convenient computerized program to help people stop smoking in about four weeks.

Participants are veterans in the New York metropolitan area. Veterans were chosen as the target population for this pilot project because they constitute a group at high risk for the ill effects of smoking. According to Dr. Schneider, past research suggests that 69 percent of veterans who use Veterans Hospitals are smokers, and pulmonary and cardiac disease are the most common medical conditions diagnosed there.

Since subjects interact only with the computer, and contact is solely through the mail, the method is private as well as convenient. This feature is targeted at those who elude other more conventional techniques because although they want to change their smoking behavior, they do not want to make a public commitment to do so.

One of the most important features of the program is that it is highly personalized—the computer sends instructions tailored to the individual behavior patterns of each subject, based on self-reported data. For example, subjects are required to keep a log of each time they smoke a cigarette and under what circumstances. Analysis of the log allows the computer to look for patterns in the subject's behavior and pinpoint any peak or "danger" times of the day when smoking is most likely.

Having to write down each time a cigarette is smoked forces the subject to be more aware that he is smoking and to decide whether he really wants the cigarette, rather than taking one simply as a reflex action.

This strategy is also often used in conventional face-to-face techniques, as are many of the other basic instructions provided by the computer. Since a change in behavior is desired, retaining old smoking habits is made cumbersome and difficult. Some of the tactics to achieve this include: restricting smoking to certain times and locations; changing brands of cigarettes; keeping them in inconvenient places; and holding the cigarette in the opposite hand.

The uniqueness of this computerized program lies in its methods of distribution of information and instructions. Since the computer analyzes the data from each subject individually, its responses are highly personalized.

Unlike in conventional face-to-face techniques, participants are not required to attend meetings, and the mail provides a convenient method of communication. However, this means that the element of peer support often provided by group meetings is absent, and awareness that there are others in the same situation often provides a framework for encouragement and mutual support. Whether these factors are significant in achieving success remains to be seen.

According to Dr. Schneider, the computerized technique has its most significant impact in the economy of time and cost required for each successful participant. Whereas face-to-face techniques require professional personnel time and must continue even if some of the subjects drop out, the computer program only involves technician time, and terminates if the subject decides to stop participation.

Preliminary results of the program indicate that approximately 38 percent of those who continued to participate after the first week did stop smoking by the end of the program. The success rate using conventional face-to-face techniques was about 55 percent. However, Dr. Schneider believes that the subjects in this computerized program would probably not have participated in other types of techniques, and therefore, the program brought about smoking cessation, economically, in 38 percent of a population that would not otherwise have been reached. Follow-up data are currently being collected and will reveal the long-term effectiveness of this method.

The concept of the program attests to other possible ways in which computers could play an important role in behavior modification techniques in various aspects of health maintenance. ■

Scientists Discuss Nutrition Link to Mental Health

Myrle Kahn

The role of nutrition in psychological health was explored at a recent NIMH workshop which focused on the potential for developing viable prevention strategies based on dietary interventions.

Scientists representing a variety of disciplines—from epidemiologists to neuroanatomists—presented their research findings in two days of discussions on "Nutritional and Dietary Interventions in Preventive Mental Health."

The work shop was sponsored by the NIMH Prevention Research Branch to focus on two growing areas of interest among mental health researchers and service providers:

- The potential that proper nutrition and other lifestyle practices have for preventing emotional and cognitive disorders.
- The usefulness of nutritional strategies in treating such disorders.

Much of the workshop's first day was spent examining the effects of maternal malnutrition on prenatal and postnatal development. Participants noted that while laboratory research with animals has demonstrated a clear link between a mother's nutrition and her offspring's brain development, these findings have yet to be applied in creating preventive strategies.

Dr. Mervyn Susser of Columbia University and Dr. G. Harvey Anderson of the University of Toronto called for further study of the role of specific nutrients in the development of specific brain structures. They also pointed to a need for more scientific data on the possible reversibiity of nutritional deficits during pregnancy.

Greater knowledge in these two areas would have a particular significance for the developing nations, the scientists said, and would be potentiailly integral to reversing America's oft-discussed "cycle of poverty."

On the second day, participants talked about links between food substances and behavior. Aware of a growing national interest in the effects of food additives, vitamins, and diets on behaviors and emotions, the researchers concentrated on separating facts from myths.

A presentation by Drs. Enoch Callaway and Iris Bell of the University of California at San Francisco sparked a discussion of the concept of "cerebral allergies," a term used to describe emotional/cognitive reactions independent of physical reactions to food substances.

The existence of such reactions has been questioned throughout the research community, and the accuracy and usefulness of the term "cerebral allergies" was the subject of a lively debate at the workshop.

Participants generally agreed that, although such reactions are rare, they do exist, and they are a critical matter to people who suffer from them. Further investigations of these "allergies" are needed, the scientists concurred, and innovative research designs will be required to identify that small but significant group of individuals who very much "are what they eat."

The importance of the workshop's focus was underscored by NIMH Director Herbert Pardes in his opening remarks. He reported that in the area of nutrition and behavior, the Institute supports 35 projects totaling nearly $2.5 million, including four projects supported through the NIMH Research Scientists Development Program.

"These projects include human studies in the areas of obesity and anorexia nervosa, as well as basic research on psychotherapeutic drugs' effects on feeding behavior," he noted. "In addition, our intramural researchers are studying the effects of caffeine and sugar on children and the effects of malnutrition on the cognitive development of the young, among other subjects."

Pardes cited a recent report of the Institute of Medicine which indicates that as much as 50 percent of U.S. mortality from the ten leading causes of death can be traced to lifestyle. "Obviously," he remarked, "dietary practices represent a significant lifestyle variable."

Later in the conference, Dr. Morton Silverman, Chief of the Prevention Research Branch, observed that lifestyle variables also encompass whether or not we smoke, how we drive, how we spend our leisure time, and even whether or not we marry or stay married.

"Direct links based on scientific and clinical data can be made between an individual's behavior and the probable quality and length of his or her life," he pointed out.

"This information has been nationally disseminated using highly sophisticated public relations strategies, yet the impact on lifestyle decisions has been far below what we would expect.

"Clearly," he concluded, "a significant issue for prevention researchers in the 1980s through the 1990s must be how to get people to accept and make use of what we learn."

A monograph of the workshop proceedings with full texts will be published by the Branch at a future date. ■

Hypoglycemia: A Hard Disorder to Diagnose, Studied by NIADDK

Linda Stalvey

Sweating, trembling, anxiety, nervousness, weakness, fatigue, and hunger are all symptoms of fasting hypoglycemia, an abnormal reduction in one of the body's essential nutrients—glucose. This potentially life-threatening metabolic state can result from a variety of causes, making diagnosis difficult.

Fasting hypoglycemia, a fall in blood glucose after six or more hours, is an extremely rare condition, and is not to be confused with the highly controversial reactive or functional hypoglycemia. In reactive hypoglycemia blood glucose falls within two to four hours after a meal. Many people wrongly believe they have hypoglycemia because of the nonspecific symptoms. This situation is further aggravated by a misunderstanding of normal blood glucose fluctuations, and by test results from the customary oral glucose tolerance test (OGTT) which are easily misinterpreted.

Fasting hypoglycemia can be caused by potentially more serious conditions such as tumors, inborn errors of metabolism, and autoimmune endocrine disease. Dr. Simeon I. Taylor, clinical investigator in the Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), has studied a novel case which puts forth another probable cause for the disorder.

In contrast to what is normally expected, Dr. Taylor has found that in certain populations of hypoglycemic patients, particularly those with autoimmune disorders such as thyroiditis and systemic lupus erythematosus (lupus), the causative factor in hypoglycemia may be autoantibodies directed against the insulin receptor.

Insulin is the major fuel-regulating hormone in humans. It is secreted into the blood in response to increased glucose and amino acid concentrations. Insulin causes circulating blood cells to take up the excess glucose, and also allows for glucose storage in liver, skeletal muscle and adipose tissue. It also promotes protein synthesis from amino acids. These actions clear the excess glucose and amino acids from the blood stream, returning elevated levels to normal.

To become biologically active, insulin must bind to a receptor located on a cell membrane. The insulin antireceptor antibody can also bind to the receptor. When this occurs, three things may happen: the antibody mimics the activity of insulin; the antibody blocks the binding of insulin to its receptor; or it desensitizes target tissues, such as the blood cells, fat cells, and muscle tissue, to insulin's effects.

In the first instance, the binding of antibody to receptor causes insulin-like effects, or a lowering of blood glucose. In the latter two instances, an insulin resistant state occurs. In insulin resistance, insulin is present, but its effectiveness is decreased, and glucose levels remain elevated.

In most patients with known anti-receptor antibodies, insulin resistance is generally the result. In Dr. Taylor's patient the converse was shown.

Through a series of specific tests, the patient was shown to have autoantibodies to the insulin receptor. When bound to the insulin receptor those antibodies mimicked the effects of insulin by lowering blood glucose levels.

This finding is particularly important to the diagnosing physician, because one cause of hypoglycemia, which is difficult to diagnose, is insulinoma. Insulinoma is a tumor of the pancreatic beta cells, which produce insulin. The treatment for this is surgery. By examining patients for anti-receptor antibodies, unnecessary surgery may be avoided.

This research also stimulates additional questions, such as what mechanism determines whether the antireceptor antibody will have an insulin-mimicking or insulin-blocking effect. Further investigation of the problem may provide important insight into the mechanism of insulin action, as well as the cause of insulin resistance.

Dr. Taylor and his colleagues reported these findings in the December 2, 1982 *New England Journal of Medicine.* ■

Scientists Understand the Function of Molecules by Developing a New Computer Program

Linda Stalvey

Living organisms have a coding system to transmit messages, not unlike a biological "morse code." Biological messages are stored in the genetic material deoxyribonucleic acid, or DNA. The code is composed of a four-letter language of nucleic acids which translates into a 20-letter language of proteins.

Proteins are the most abundant molecules in cells. They are located in every part of every cell, and are specialized for different biological functions. Most of the genetic information in a cell is expressed by proteins. Proteins are used for transport (hemoglobin), for nutrient storage (egg albumin), for muscle contraction (actin and myosin), for body protection (blood clotting factors), and as structural elements (collagen). Enzymes and many hormones are also proteins.

As scientists work to unravel genetic codes and protein structures, they need a quick, easy, inexpensive method to compare a nucleic acid or protein sequence produced in their labs to other known sequences.

By performing this comparison, the scientist can get important clues to the function of the molecule, or may be able to modify a structure chemically to change the function.

Recently, Drs. W. John Wilbur and David J. Lipman, of the Mathematical Research Branch, NIADDK, developed such a method. It is a computer program used to search specialized data banks, and compares one sequence of a molecule or part of a molecule to other known sequences, to point out similar segments between the sequences compared.

The program developed by Drs. Wilbur and Lipman uses the NIH DEC-KL-10 computer system and can compare the test sequence to all sequences in the entire Protein Data Bank of the National Biomedical Research Foundation or the Los Alamos Nucleic Acid Data Base. When compared to other techniques of similarity analysis, their method results in a substantial reduction in the time required to search a data bank, and it does so with minimal loss in sensitivity. The reduction in time is also a reduction in cost.

The 4-letter genetic code consists of the letters A, T, G, and C which corresponds to the nucleotides adenine, thymine, guanine, and cytosine. Certain combinations of these nucleic acids code for specific amino acids, such as the codes for the amino acids lysine, AAA, and leucine, CUC. Proteins are made of a series of amino acids. A portion of a protein sequence may look like this: DIVMTQSPSS. Proteins similar in function often have similar sequences of amino acids.

The program looks for matches of successive amino acids (for protein) or successive nucleotides (for nucleic acids). The number of successive amino acids (or nucleotides) needed for a "match" can be set by the investigator, and is usually a low number like 2, 3, or 4. This series of matches rather than single matches is critical for the increased efficiency of the method, and may possibly be more important to the biological function of the molecule. The program will also automatically insert a gap area in the sequence, if it will allow for more overall matches between two sequences. Even the insertion of a gap has biological significance. A gap may represent a genetic mutation. Based on a mathematical scoring system, "+" points for matches and "–" points for gaps, the "best" match can be made between two sequences.

This program has been used by several NIH components, including the National Cancer Institute's Laboratory of Biochemistry and the National Institute of Child Health and Human Development's Laboratory of Molecular Genetics. It is useful to anyone who has a molecule sequenced and wishes to relate it to previously known sequences. Detailed information is available by typing file RBSA.DOC[14,21,LIPMAN], or by calling Drs. Wilbur or Lipman at 496-4325.

While all sequences are not entered in the data banks, the number so entered is increasing rapidly. This program allows the computer search of existing information to become a powerful tool in understanding the mysteries of biological function. ■

Ether Lipids May Prove to Be Key to Controlling Hypertension and Tumor Development

Russ Manning

The purification of an enzyme responsible for forming ether bonds in lipids and the discovery of an ether-linked phospholipid that has strong biological activity may eventually lead to controlling such physiological malfunctions as high blood pressure and the growth of tumors.

Since the early 1960s, researchers at the Medical and Health Sciences Division of Oak Ridge Associated Universities (ORAU) have been studying the role of lipids in biochemical processes. Current studies, supported by the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the U.S. Department of Energy, are focused on the synthesis and catabolism of ether lipids.

Found throughout the body, complex lipids were once thought to have little function other than as structural components of cell membranes; several forms contain ether linkages. But in the mid-1960s, ORAU's lipid biochemistry group headed by Dr. Fred L. Snyder found high levels of a specific type of ether lipid, the alkyldiacylglycerols, in tumor cells.

An interest in anything differentiating tumor cells from normal cells kept alive research into the function of lipids at a time when no one knew if these kinds of lipids had any biochemical function. By understanding the differences, researchers hoped to learn the mechanisms transforming normal to cancerous tissue.

So for many years, NCI funded the research at ORAU on the enzymes responsible for the synthesis and regulation of ether lipids. The studies resulted in 1980 in the purification of the enzyme responsible for formation of the ether bond. The enzyme is referred to as alkyl-DHAP synthase (alkyldihydroxyacetonephosphate synthase).

"The purification of the enzyme is an important step," explains Snyder, who is also Associate Director of ORAU's Medical and Health Sciences Division, "because that gives us an opportunity to study the regulation of this enzyme and the factors that control its activity. We may then be able to explain why ether-linked lipids are high in some cells or parts of cells and not in others."

The purifications was done in the laboratory by Dr. Alex Brown, at the time working under Snyder as a graduate student in the University of Tenessee-Oak Ridge Graduate School of Biomedical Sciences; he currently works under a fellowship from The Mellon Foundation in ORAU's medical division. "The difficult step was to solubilize the enzyme using detergents and then to extract it with organic solvents," Brown says. "Once that had been accomplished, we used routine purification procedures—ion exchange and other chromatography techniques—to get a 1000-fold purification so far."

With the purified enzyme, ORAU biochemists have been able to determine the order in which the substrates bind to the enzyme and the order in which the ether-lipid products are released, information that was formerly hidden by the activity of competing enzymes. "There were claims that this enzyme catalyzed other reactions," says Brown, "for example, that it could hydrolyze the substrate as well as convert it to the normal products. We were able to show that is not the case and that the data supporting that claim were due to the presence of contaminating enzymes."

Another enzyme responsible for the formation of ether-linked lipids is under investigation by Dr. Ten-ching Lee, a biochemist in ORAU's medical division. Lee is attempting to ascertain if hormones can induce the production of acyl-CoA reductase, the enzyme that produces the fatty alcohol precursor that is an ingredient in the formation of ether lipids. She has found that the production of acyl-CoA reductase is stimulated by testosterone.

Through such studies, says Lee, "we hope to learn more about the properties of acyl-CoA reductase, like how long it takes to be synthesized and degraded. From our understanding of how the enzyme works we expect to eventually learn how it can be regulated." Lee uses the mouse preputial gland as an experimental model in her work because, like tumor tissue, these glands produce high amounts of ether lipids.

As a graduate student, Alex Brown, now a Mellon Fellow, succeeded in purifying the enzyme that makes the lipid ether bond. This enzyme preparation has since been used in kinetic and substrate mechanistic studies of ether bond-forming reaction. NIH PHOTO 1853

The NCI studies are now in their thirteenth year. Although basic studies into the role of alkyl-DHAP synthase in forming ether lipids will continue, the ultimate goal is to be able to predict and to control, or inhibit, the growth of tumor cells. It is possible that the enzyme may be used as a preneoplastic indicator if the enzyme concentration is found to increase before a tumor develops. Or if ether lipids are somehow involved in the transformation of normal cells to tumor cells, a way may be found to inhibit the ether-lipid synthesis by controlling the activity of the enzyme, thus inhibiting the growth of tumors.

Adjunct to this work with ether lipids and the enzyme that forms the ether bond was the discovery in the late 1970s of the ether phospholipid that is very biologically active. In collaboration with Dr. E. E. Muirhead, Professor and Chairman of the Pathology Department at the University of Tennessee Center for the Health Sciences in Memphis, ORAU's lipid biochemistry group was investigating a biologically active compound that lowered blood pressure in experimental rats.

At the same time, two other research groups at institutions in Texas and France were studying a lipid substance known as "platelet-activating factor (PAF)." With support from NIH, the San Antonio group headed by Dr. Donald J. Hanahan, Professor and Chairman of the Biochemistry Department of the Health Science Center of the University of Texas, isolated natural PAF from stimulated rabbit basophils.

In the fall of 1979, all three groups published papers identifying the compounds they had been studying and found that in each case the compound was the same, a phospholipid, 1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine, abbreviated alkylacetyl-GPC. Subsequent research confirmed it is a powerful biological activator, having not only antihypertensive and platelet-aggregating activity but also capable of affecting allergic and inflammatory responses.

Dr. Snyder recalls that "no one knew that molecules of this sort could have such potent biological activities." Similar phospholipids are major ingredients of all cell membranes, he explains, "but alkylacetyl-GPC is the only naturally occurring phospholipid known to mediate chemical and physical changes in body processes."

At ORAU the phospholipid was prepared semisynthetically from beef heart. Merle L. Blank, a biochemist with ORAU's Medical and Health Sciences Division, says "a little luck was involved in determining the structure of the compound."

Using such analytical data as nuclear magnetic resonance, chemical, and mass-spectral information, the researchers guessed the structure of the phospholipid. They then synthesized this phospholipid they suspected of causing the activity and found it had the same kind of activity as the mixture of compounds they had been studying. "The first structure we tried was correct," says Blank.

In studying the inflammatory properties of alkylacetyl-GPC, Dr. Albert uses a thin-layer chromatographic technique to quantitate the active lipid released by stimulated alveolar macrophages.

NIH PHOTO 1854

In 1980 the National Heart, Lung, and Blood Institute began funding the ORAU study of the biochemical properties and mechanism of action of alkylacetyl-GPC.

Since then the lipid biochemistry group has tested several phospholipid analogs to see if molecules of similar structure have the same biological activity as alkylacetyl-GPC. The tests were conducted on SHR rats, experimental rodents which spontaneously develop hypertension. One compound was found to be equally active, an ether phospholipid with a propionate group rather than an acetate group attached to the second carbon. According to Blank, the biological activity seems to require a short-chain carbon group in that second position because attaching longer chains than propionate causes the activity to decrease.

"But it's not just the acetate or propionate group that produces the activity," Blank explains, "the whole molecule is required to get the biological activity. When we substituted another base for the choline, the activity decreased. If we substituted a fatty acid group for the long-chain ether at the first carbon position, again we lost the activity. The alkylacetyl-GPC molecule is very specific for maximum biological activity."

Because the structure of alkylacetyl-GPC is so specific for its biological activity, the possibility arises that learning to control its metabolism may lead to manipulating its concentration in the body. Dr. Myles C. Cabot, another ORAU biochemist, has been investigating the metabolism of alkylacetyl-GPC in various cells—mouse fibroblast, leukemia, and kidney cells—specifically looking for enzyme activity that would remove the acetyl group from the alkylacetyl-GPC molecule, rendering it inactive. "There are enzymes in cells or in blood that can easily make alkylacetyl-GPC inactive," says Cabot, "so it's important to characterize the enzymes and to find what factors control them."

The lipid biochemistry group found in serum an extremely active acetylhydrolase, an enzyme that removes the acetyl group, producing the lyso form of the molecule and making it biologically inactive. In related experiments, alkylacetyl-GPC hydrolase from rat kidney cells was partially purified. Although it has similar activity to the hydrolase found in serum, the researchers do not yet know if the two enzymes are the same.

Left to right, Myles Cabot, Merle Blank, Fred Snyder, and Ten-ching Lee examine a model of alkylacetyl-GPC, a platelet-activating, hypotensive phospholipid that is the subject of their investigations. NIH PHOTO 1855

By looking at several animal species, the ORAU biochemists found that the activity of the serum enzyme varies widely among species. They are now working to determine if the serum hydrolase activity is involved in the body's responses to PAF-stimulated platelets, with the hydrolase possibly regulating the responses.

"If the enzyme that removes the acetyl group in fact regulates alkylacetyl-GPC once it's synthesized, that enzyme is very important," says Cabot. "For therapeutic purposes, it may eventually be possible to synthesize some compound that would inhibit the acetylhydrolase, thus increasing the level of alkylacetyl-GPC in the bloodstream."

In other studies using rabbit platelets to test changes in calcium uptake, Ten-ching Lee has been investigating the mechanism of platelet activation of alkylacetyl-GPC, which can be measured by serotonin release. Rabbit platelets are used because they require extracellular calcium, whereas only internal calcium is mobilized during activation of human platelets.

"We looked at the sequence of events," says Lee, "to see if it's the calcium level that causes the reaction of serotonin release." After finding that the phospholipid can increase the calcium uptake in platelets, the biochemists have speculated that alkylacetyl-GPC might exert its biological effect by increasing calcium permeability in platelets.

Also, alkylacetyl-GPC may be involved in immune responses to various pathogens, according to Dr. Daniel H. Albert, a Mellon Fellow with ORAU's lipid biochemistry group. "We don't know the function of this phospholipid, but there are indications it has some function in inflammatory responses, such as natural defenses against pathogens and foreign proteins. This lipid may have a role in the recruitment of other cells to the affected area and in the release of other imflammatory mediators."

So under the NHLBI grant, Albert has been studying alveolar macrophages, scavenger cells in the lungs that are responsible for part of the body's defense against pathogens and particulate matter. When stimulated during phagocytosis, in which inhaled bacteria or pollutant particles are engulfed, macrophages release lipids, including alkylacetyl-GPC.

Using rat alveolar macrophages in his experiments to understand the synthetic pathway of this phospholipid, Albert has found that macrophages contain a substantial pool of the phospholipid's precursor, alkylacyl-GPC, which has a long-chain fatty acid in the second carbon position rather than the acetate group. "I've been able to label that pool," says Albert, "by giving the cell a precursor lipid tagged with tritium. The macrophages take this up and the lipid equilibrates in the endogenous precursor pool. I can then stimulate the cells and follow the metabolism of the precursor."

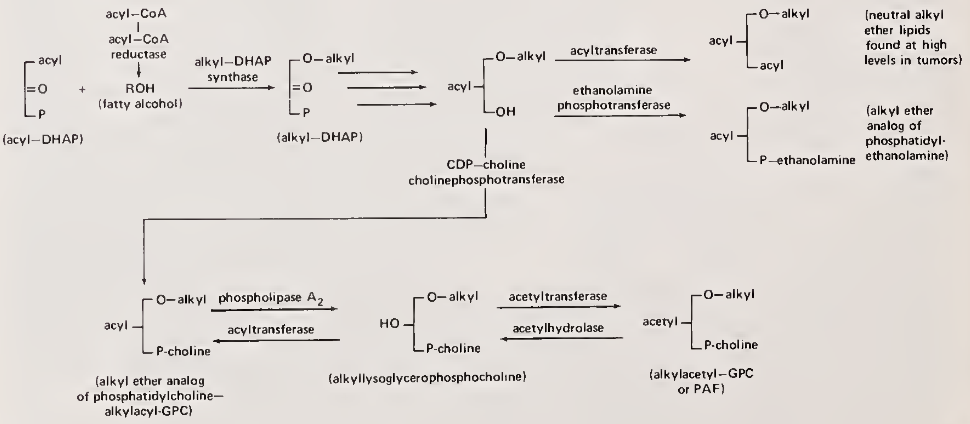
Through these studies, the lipid biochemistry group has shown that two enzymes, phospholipase A and acetyltranferase, are involved in the synthesis of alkylacetyl-GPC from its precursor, alkylacyl-GPC, and that these enzymes are activated under the same conditions that stimulate the release of alkylacetyl-GPC from macrophages. So it appears that it is the stimulation of these two enzymes that regulates the synthesis of the active phospholipid, since a substantial pool of the precursor exists in the cells.

As it turns out, a substantial portion of the long-chain fatty acids found in the second carbon position of the precursor molecule is arachidonic acid, a precursor of another class of inflammatory mediators that includes prostaglandins and other bioactive metabolites derived from arachidonic acid. "So it may be," says Albert, "that the precursor of alkylacetyl-GPC is also an important source of arachidonic acid in the enzymatic reaction that catalyzes the release of this fatty acid, which is the first step in the formation of arachidonic-derived mediators." This has pharmacological significance because it is thought that anti-inflammatory drugs work by inhibiting prostaglandin biosynthesis, possible through blocking the release of arachidonate from phospholipids.

But alkylacetyl-GPC itself is a very active molecule, and ORAU researchers think there should be some way of controlling its synthesis, release, and metabolism in the cell, since such a potent molecule cannot be present and active all the time. So under the support of NHLBI, the lipid biochemistry group of ORAU's Medical and Health Sciences Division will continue their studies in the metabolism and regulation of alkylacetyl-GPC. Eventually, these studies may lead to ways to control hypertension, blood clotting, and allergic and inflammatory responses. ■

ORAU 8328

BIOSYNTHETIC PATHWAY FOR ALKYL ETHER LIPIDS IN THE FORMATION OF BIOACTIVE PHOSPHOLIPID SPECIES



NIH PHOTO 185

Photos Courtesy of Oak Ridge Associated Universities

Medical Capsules

Sandra D. Levine

- There is evidence that not only smoking tobacco is carcinogenic, but that chewing tobacco and using snuff may also cause cancer. Research by the National Cancer Institute (NCI) shows that young people who chew tobacco or use snuff are at a much greater risk of developing cancer of the mouth than those who do not.

- The natural instinct of animals to lick their wounds may teach scientists about the processes involved in healing. NIH has been funding studies at the University of Florida College of Medicine to investigate the wound-healing effects of "nerve growth factor" (NGF)—a protein contained in the saliva of some animals. NGF is believed to help activate a specific part of the natural immune system which is composed of a series of proteins in the blood that fight disease.

- Researchers at the University of New Hampshire have been awarded a three-year grant by the National Cancer Institute (NCI) to study how certain chemicals can inhibit the development of malignant breast tumors in animals. The research includes designing a mathematical model to trace the transformation of a normal cell into a cancerous one.

  Since breast cancer is the primary cause of death from cancer among women in this country, the investigators hope that their findings will have relevance for prevention of these malignant tumors when applied later to human populations.

  The study is part of a new NCI program to explore the area of chemoprevention.

- Over 20,000 physicians nationwide are taking part in a Brigham and Women's Hospital/Harvard Medical School study to determine whether regular aspirin consumption can reduce total all-cause as well as cardiovascular mortality, and whether beta-carotene (a precursor to vitamin A) can reduce the risk of cancer.

  The participants, all males aged 40 to 75, are taking on alternate days for four years a tablet (either aspirin or placebo) and a capsule (either beta-carotene or placebo).

  This randomized, double-blind trial is supported by both the National Heart, Lung and Blood Institute and the National Cancer Institute.

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April 1983

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MAY 23 1983
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NIH PHOTO 1857

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News&Features from NIH

April 1983

Suicide is the third leading cause of death among people aged 15 to 25. The causes and some means of prevention were examined recently at a workshop in Cambridge, Massachusetts.

Factors which seem to put young people at high risk for suicide include: feelings of isolation and loneliness; depression; stressful or nonsupportive family relationships; and low self-esteem.

Suggestions for prevention include developing multi-faceted programs to deal with the many aspects of suicide in young people, geared to their specific needs and developmental levels. See page 8

There are several new advances in kidney research, in both the areas of transplantation and dialysis.

One recent development includes the use of the anti-rejection drug, cyclosporine, which has been successful in several types of organ transplants. Another development is pre-transplant blood transfusions which enable a kidney to be used from a donor who has some genetic differences from the recipient. See page 3

Over a quarter of a million children suffer from juvenile arthritis, a group of chronic conditions characterized by inflammation of the joints. Early diagnosis is difficult because the signs and symptoms vary and often mimic those of other illnesses.

There is no known cure, but juvenile arthritis can be controlled by medical and physical therapy. Since it is multi-faceted, a team approach to treatment is often favored.

An important area of research is focused on isolating genetic markers so that children predisposed to the disease can be identified and treated before they experience serious complications. See page 6

The National Institute of Dental Research (NIDR) is investigating the use of a computer which permits three-dimensional images of teeth to be seen from only eight x-rays taken from different angles.

Since these three-dimensional images show slices of tissue, they enable details to be seen that are impossible to visualize with conventional x-rays.

With more research, it is hoped that this computerized x-ray technique could eventually become a possible alternative to conventional radiographic methods. See page 9

Paralytic polio is still a major problem in many parts of the world, affecting one in every 200 children.

At a recent International Symposium on Poliomyelitis Control, attended by both Drs. Jonas Salk and Albert Sabin, it was felt that polio can be controlled worldwide using the Salk and Sabin vaccines. The complete eradication of polio, however, cannot be achieved until effective control programs are implemented in developing countries where the disease is still prevalent. See page 2

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Editorial Staff
Susan Gerhold
Acting Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

NIH News Branch
Building 31, Room 2B-10
Bethesda, Maryland 20205

Phone:
(301) 496-2535

Polio Disappears Throughout the United States But Still Lingers Overseas

Dr. John Burke

Paralytic polio has been essentially eradicated in the United States but not in 65 percent of the other nations in the world.

In the U.S., polio has been controlled mainly through the use of vaccines, most notably those perfected by Dr. Jonas Salk and Dr. Albert Sabin, both of whom attended and presented papers at the recent International Symposium on Poliomyelitis Control. The symposium was sponsored by the Fogarty International Center (FIC) in collaboration with several Institutes at NIH, the World Health Organization, the Centers for Disease Control (CDC) and other groups.

At the meeting, it was concluded that polio can be controlled worldwide with the use of the Sabin and Salk vaccines, but that eradication of polio (elimination of the viruses) is not feasible at this time. However, this remains a distant, though achievable, goal.

At present, one of every 200 children born will suffer paralytic polio.

The immediate prospect for developing countries is more—not less—polio, unless and until they adopt effective control programs, it was noted. This was the pattern in developed countries prior to the widespread use of vaccines.

The symposium concluded that "the problems facing control of polio in warm countries are administrative rather than technical . . . The overriding need is for political commitment to polio control."

It was recommended that countries in which polio is a major problem be assisted in developing programs adapted to their needs and that these programs be started now.

It was also recommended that further support be given to the goal of incorporating vaccination programs into routine health services.

However, such services are not adequate in many parts of the world at present, and consideration should be given to special programs where major changes can be made in a short period of time.

Great interest in the impact of poliomyelitis vaccines has arisen as a result of significant scientific advances that were discussed at the symposium.

These include development of an extraordinarily potent and effective inactivated polio vaccine (IPV), and the encouraging results arising from recombinant DNA technology, as reported by Nobel Laureate Dr. David Baltimore and other speakers.

Concern had been expressed regarding the mutation of attenuated (live) poliovirus and the rare occurrence of vaccine-associated cases of paralytic poliomyelitis.

It now appears possible to produce an attenuated vaccine that could not revert to virulence because of deletion of the virulence genes.

The potential use of such a vaccine remains problematic at this time because of ethical and practical difficulties in view of the availability of the safe, effective, and widely used Sabin and Salk vaccines.

Clear evidence was presented that the Sabin oral polio vaccine (OPV) has controlled poliomyelitis in the tropical world, but—in certain situations—OPV has not proved as effective as in temperate climates. The reasons are still not well understood.

Practical results from recent research in molecular biology were reported at the symposium. For example, it is now possible to trace epidemiologic links between polio cases through oligonucleotide finger-printing.

That is, during epidemics the poliovirus isolates can be traced geographically, and vaccine-associated strains can be distinguished from wild poliovirus strains which, in turn, can be distinguished from one another. However, the evolutionary range is very short, and only very similar viruses can be related.

Although there are scheduling problems with a combined DPT (diphtheria-tetanus-pertussis)—poliomyelitis vaccine, it is believed that these can be worked out satisfactorily to achieve the necessa protective immunity.

Currently there is major variation in the performance and results of neutralizing antibody tests in different laboratories. It was recommended that international cooperation in standardization be encouraged. Increasing the stability of poliovirus vaccines was considered a problem that also merits resolution.

In the concluding session, it was suggested that the new science of "vaccinology"—the development of new vaccines—be pursued vigorously.

The use of recombinant DNA techniques in producing these new vaccines offers great promise in terms of benefiting other disease areas and moving science ahead.

Proceedings of the symposium will appear as a supplement in a forthcoming issue of the *Reviews of Infectious Diseases.* ■

Members of the panel at the recent International Symposium on Poliomyelitis Control are left to right: Dr. Ralph Henderson, WHO; Dr. Frederick C. Robbins, National Academy of Sciences; Dr. Dorothy M. Horstmann, Yale University School of Medicine; and Dr. John P. Fox, University of Washington, at Seattle.

NIH PHOTO 1858

Drs. Sabin (left) and Salk both attended the recent polio conference held in Washington, D.C.

NIH PHOTO 185

New Advances in Kidney Research Discussed at Recent Foundation Meeting

James Fordham

New advances in transplantation, dialysis and kidney research was the subject of a recent one-and-a-half day news briefing sponsored by the National Kidney Foundation in Washington, D.C.

More than a dozen leading scientists explained recent research developments considered of vital importance to the more than 13 million Americans who suffer from diseases of the kidney and urinary tract.

Dr. John S. Najarian, Chairman of the Department of Surgery at the University of Minnesota Hospitals, told the press that "One of the most exciting new developments in transplantation is the anti-rejection drug cyclosporine." He described clinical trials supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) that show that use of cyclosporine A in kidney transplant patients improved graft survival, cutting the number of rejection episodes in half. The rate of infection in these operations was also sharply reduced.

"Subsequently, we have used this material in our liver, pancreas and heart transplant program and found it to be equally impressive, particularly in the diabetic patients who receive pancreas transplants," Dr. Najarian said. "These patients don't do well with the usual high doses of prednisone, a cortisone, which makes their diabetes worse. This has allowed us to develop a quite successful pancreas transplant program for diabetics. We have currently transplanted 62 patients with type I juvenile onset diabetes. In addition, we have used this agent for our liver transplant program and found it to be very effective, specifically when transplanting small children, where it is even more important not to have associated problems with infection."

Kidney damage resulting from diabetes is the most prevalent, debilitating, and costly form of kidney disease in the U.S., according to Dr. Eli A. Friedman, Professor of Medicine at the Downstate Medical Center. He said the proportion of new dialysis patients who are diabetic has increased to approximately one in four.

"Diabetic nephropathy, previously viewed as untreatable," said Dr. Friedman, "has gradually yielded to a combined medical surgical approach. Kidney transplantation, continuous ambulatory peritoneal dialysis, and hemodialysis are all capable of producing rehabilitation for a substantial proportion of uremic diabetics." He said that regulation of blood glucose combined with strict attention to avoiding hypertension is the key to greatly improved survival and rehabilitation in diabetics on dialysis or receiving a transplant. He suggested that advances in [illegible] continuous normalization of blood sugar might eventually lead to prevention of diabetic nephropathy and renal failure.

Dr. James A. Roberts, Professor of Urology at Tulane Medical School said that he and his colleagues have found that urinary tract infections, if not detected and treated during the early stages, may lead to kidney infection (pyelonephritis) with renal scarring and loss of kidney function. Dr. Roberts described his research, supported by NIADDK, showing that the sequence of events that lead to renal scarring are: (1) infection occurs when P-fimbriated bacteria (hair-like structures on their surface) stick to cells of the urinary tract; (2) bacterial toxins paralyze muscular function of the ureter, and infection spreads to the kidney; and (3) white blood cells attack bacteria by releasing toxic oxygen metabolites, causing loss of renal tissue and loss of renal function.

An important result of clinical and laboratory studies following discovery of these processes by the NIADDK grantee has been development of a diagnostic testing kit for P-fimbriae by scientists in Sweden who collaborated with Dr. Roberts' group. "The test provides rapid diagnosis, is easily done, and requires no special equipment." said Dr. Roberts. "Since the Swedish group has shown that 95 percent of the children suffering from first episodes of pyelonephritis are infected with P-fimbriated bacteria, its detection in a urinary tract infection is the signal that vigorous and immediate treatment is necessary if renal infection is to be avoided or eradicated."

He pointed to the eventual emergence of new therapies from this research, such as development of a drug to prevent attachment of the bacteria to the urinary tract cells, administration of the enzyme superoxide dismutase (which decreases the effect of toxic oxygen metabolism), and immunization with purified fimbriae.

Dr. William J.C. Amend, Jr., Clinical Professor of Medicine at the University of California at San Francisco discussed the latest technique of pre-transplant blood transfusion, which enables doctors to perform successful kidney transplantation from a donor with pronounced genetic differences from the recipient.

Dr. Amend described the donor-specific transfusion technique, developed in recent years with NIADDK support, in which 200cc of whole blood is collected from the prospective donor and administered to the renal patient. This procedure is carried out on three separate occasions, at least two weeks apart. Serum samples are taken before each transfusion, and again two weeks later, to determine whether antibody responses against white blood cells of the donor have been produced in the renal paient. If anti-donor T-cell antibodies are produced in the patient after the three transfusions, the transplant is not performed. It is performed, however, if transient B-cell antibodies (but not T-cell antibodies) are found, or if no T and B antibodies are found.

Dr. Amend said this technique offers excellent rehabilitation results for patients with chronic renal failure. In the near future, large numbers of patients might be able to receive successful transplants from living non-relatives, such as spouses and friends. "More importantly," he said, "we hope to apply the lessons from this experience so that we may more successfully condition kidney failure patients to receive cadaver transplants."

The problem of chronic kidney disease resulting from excessive use of "over-the-counter" pain medication mixtures containing aspirin, acetaminophen and phenacetin was discussed by Dr. William M. Bennett, Head of the Division of Nephrology/Hypertension at the Oregon Health Sciences University.

Some physicians as well as patients are unaware of the long-term consequences of non-prescription analgesics, according to Dr. Bennett. "Rather than being completely safe as advertisements imply," he said, "these drugs when taken regularly may produce progressive kidney scarring and eventually kidney failure."

Many people take these compounds daily for minor aches and pains, or for the mild mood-altering properties of the drugs. "In the United States as many as five to ten percent of all patients entering into some end-stage kidney disease programs for dialysis or transplant care have analgesic nephropathy, although usually the diagnosis is missed or mistakenly attributed to some other cause," said Dr. Bennett.

He called for more research to increase scientific understanding of the mechanisms of injury from these drugs so that preventive measures can be taken. He also discussed the hazard of exposure to occupational sources of lead that may cause kidney damage. If chronic lead toxicity is diagnosed early, he said, chronic kidney disease can be prevented.

Further research developments discussed at the briefing included: new techniques for the treatment and removal of kidney stones; experimental therapies against the deleterious effects of immune injury on the kidney (glomerulonephritis); use of the calcium blocking drug Verapamil to prevent acute renal failure; work of NIADDK grantees using monoclonal antibodies to reverse rejection processes in transplantation; the introduction of continuous ambulatory peritoneal dialysis (CAPD) to treat children requiring prolonged dialysis; and the role of nutritional therapy in renal disease. ■

Basal Forebrain Holds Clues to Alzheimer's Disease

Prepared by the Office of Scientific and Health Reports, NINCDS

NINCDS grantee Dr. Donald Price, Professor of Pathology and Neurology at Johns Hopkins University, points to the brain area in which he and his associates identified damage to cholinergic neurons in patients with Alzheimer's disease. NIH PHOTO 1860

A research team at The Johns Hopkins University School of Medicine has discovered that patients with Alzheimer's disease show abnormalities in a specific population of cholinergic nerve cells deep in the basal forebrain. This important finding indicates that Alzheimer's disease—like Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other degenerative disorders—is characterized by the dysfunction and death of specific groups of nerve cells in the brain.

The research was carried out in the University's Neuropathology Laboratory under the leadership of Dr. Donald Price, Professor of Pathology and Neurology.

The study was funded by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), and the National Institute on Aging (NIA).

According to Dr. Murray Goldstein, NINCDS Director, the finding of a specific brain lesion in Alzheimer's disease is important in shaping a more accurate perception of the disease. "This finding provides meaningful evidence that Alzheimer's disease is an organic brain disease, not primarily a psychiatric or psychosocial problem," Dr. Goldstein says.

Describing the findings at a meeting of the NINCDS Advisory Council in January, Dr. Price cautioned that the discovery will not lead to an immediate treatment for Alzheimer's disease. "It would be premature to attempt to devise a rational therapy for Alzheimer's disease, because we do not yet know enough about the disease or the various neuronal systems involved in the disorder," he said.

However, he pointed out that there is increasing evidence that at early stages of the disease therapies may be possible. "There appears to be a prolonged period during which brain cells are functioning abnormally," Dr. Price told the Council. "At that stage, the disease may be potentially reversible."

Dr. Price said he believes that his team's new findings will, in turn, stimulate work designed to clarify the functions of the involved brain region. "I predict that in the next 10 years we will know a great deal more about the neurobiology of the basal forebrain cholinergic system, its functional organization, and its role in memory and cognition."

Alzheimer's disease is a disabling neurological illness that affects approximately 5 percent of all persons over the age of 65 and a lesser number of younger people. It is characterized by abnormalities of memory, thought, orientation, and behavior. With demographers predicting a large increase in the elderly population over the next 20 years, it is clear that Alzheimer's disease will become an increasingly important cause of chronic illness.

The condition was first described in 1907 by the German physician Alois Alzheimer who recognized the clinical syndrome and two of the neuropathological features that remain the disease's hallmarks: neurofibrillary tangles and neuritic plaques.

Neurofibrillary tangles are accumulations of paired helical filaments within nerve cells bodies. Neuritic plaques are commonly seen in the cerebral cortex, and consist of clusters of nerve endings surrounding a core of extracellular amyloid. As individual plaques evolve, there appears to be a loss of nerve endings thought to represent degeneration of nerve fibers.

In the mid-1970's, several groups of neurochemists, including Drs. Peter Davies (Albert Einstein College of Medicine) and David Bowen (Queen Square Hospital) discovered that the brains of Alzheimer's disease patients showed a selective loss of enzymes important in the metabolism of the neurotransmitter acetylcholine (ACh). The enzyme that synthesizes ACh and the enzyme that degrades ACh were both reduced in the cerebral cortex of Alzheimer's disease patients. Because ACh carries messages from one nerve cell to another, investigators suspected that loss of cholinergic transmission might be implicated in the clinical symptom of dementia.

An important new question then arose: Where in the brain are located the neurons that project to the cortex and use ACh to transmit messages?

A nerve cell is composed of several parts: the cell body contains the genetic information and protein-synthesizing machinery; dendrites receive inputs from a variety of sources; the axon extends long distances and carries electrical impulses; and synapses, or nerve terminals, are the sites at which one neuron communicates with another by liberati[illegible] a specific neurotransmitter. Beca[illegible] nerve fibers are so long, and because there are so many bundles of them intertwined within the brain, it is difficult to tell which nerve fibers derive from which cell bodies.

Based on observations from animal studies conducted by many investigators over the years, Dr. Price and his colleagues suspected that the cholinergic deficits in Alzheimer's disease might result from abnormalities of the basal forebrain system. They hypothesized that the nucleus basalis of Meynert might be the source of cholinergic innervation in the cortex. If this hypothesis were true, autopsy studies of the nucleus basalis of Meynert of persons who died with Alzheimer's disease might show a loss of nerve cells in this region.

At this stage of the investigation, Dr. Price recalled, serendipity intervened.

In 1980, Drs. Peter Whitehouse, Price, and coworkers in the Neuropathology Laboratory at Johns Hopkins had the opportunity to examine the basal forebrain of a 74-year-old man who had died after a 14-year history of progressive dementia. Moreover, he had a strong family history of Alzheimer's disease.

When the investigators compared

tions of this man's brain with sections of brain from patients who had died of other causes, it was obvious that the brain of the demented patient was very different. The loss of nerve cells in the basal forebrain was so severe, said Dr. Price, "we could see the differences with the naked eye." Precise measurements revealed that 95 percent of neurons in the nucleus basalis [illegible] Meynert had degenerated.

The Johns Hopkins team is now examining the brains of Alzheimer's patients who did not have a family history of the disease, and has shown that they too have a substantial loss of cholinergic neurons in the basal forebrain.

Dr. Price emphasized that "the clues to understanding Alzheimer's disease have come from basic neuroscience."

"When we started this research, it was not even known that the nucleus basalis was cholinergic. Without the knowledge gained by other investigators studying the basal forebrain in animals, it is not likely that this brain region would have been investigated in humans."

He pointed out that several investigators, including Drs. Michael Johnstone, Michael McKinney, Joseph Coyle, and John Lehmann at Johns Hopkins, had shown that lesions in the rodent ventral forebrain have cholinergic deficits in cortex. "The similarities of these neurochemical changes to those in the brains of Alzheimer's disease patients were another clue to the possible role of this system in this type of dementia," Dr. Price said.

More recently, investigators in the Johns Hopkins Neuropathology Laboratory have extended these findings to investigate the possible role of the nucleus basalis of Meynert in the development of neuritic plaques. Knowing that aged monkeys developed neuritic plaques, Drs. Robert Struble and Linda Cork began a systematic study of the brains of aged monkeys who had been untreated controls in a long-term experiment on the effect of radiation in primates. When the scientists looked at the brains in these animals, they found three stages of neuritic plaques. In the earliest type of plaque, there were enlarged nerve terminals and only a little amyloid. Intermediate-stage plaques contained moderate amounts of both nerve endings and amyloid. The more advanced or "burned-out" plaques contained only a few nerve fibers and a great deal of amyloid.

Special staining techniques disclosed changes in acetylcholinesterase (AChE) activity in plaques as they evolve. AChE is the enzyme that causes ACh to break down, and is a useful marker for studying the distribution of nerve terminals coming from the nucleus basalis of Meynert. Immature plaques were rich in AChE, while "burned-out" plaques showed lesser amounts of enzyme activity. This finding suggests that the axons and nerve terminals derived from the nucleus basalis of Meynert are at least one population of nerve terminals in the plaque and that these nerve terminals gradually disappear as the plaque evolves.

According to Dr. Price, "These observations may be explained by a slow degeneration of axons and nerve terminals derived from the nucleus basalis."

Dr. Price said he believes that this is just the beginning of the story. Investigators at Johns Hopkins are actively pursuing this research. Drs. Mahlon R. DeLong, Susan J. Mitchell, and John Lehmann have destroyed basal forebrain cells in monkeys and have begun to look at chemical and anatomical alterations in cortex.

Dr. Price cautioned, however, that this acute lesion does not faithfully mimic Alzheimer's disease, which is a chronic, progressive illness.

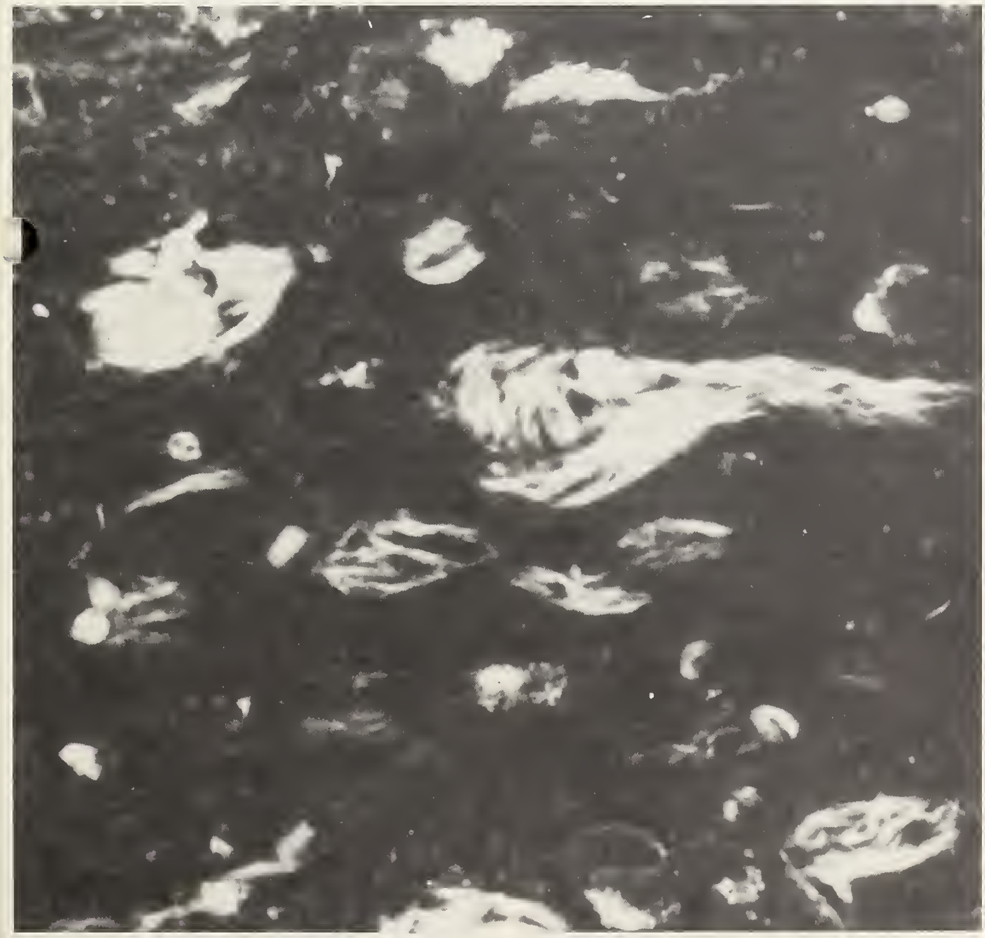
"Alzheimer's disease is not like polio," he explained. "In polio, a virus gets into the nerve cell and kills it within 24 to 48 hours. We believe this acute process does not occur in Alzheimer's disease—nor in Huntington's disease, amyotrophic lateral sclerosis, or the other chronically progressive degenerative disorders."

So Dr. Price and his coworkers are searching for ways to produce more chronic pathology in the basal forebrain in order to simulate more closely the course of brain damage in Alzheimer's disease.

It may take some time before these advances are translated into effective therapies. Although Dr. Price agreed that "selected clinical trials are important," he proposed that "money, time, and effort would be well invested in studies designed to obtain basic information about the systems implicated in Alzheimer's disease so that more rational therapies can be designed."

"There has been an extraordinary resurgence of research interest in Alzheimer's disease," Dr. Price told the NINCDS Advisory Council. "One of the most important components of this resurgence has been the commitment of a number of bright, young investigators to this field. With adequate support, I think we can be certain that over the next few years these talented young physicians and scientists will make important advances in our understanding of Alzheimer's disease."

The research on the cholinergic system in Alzheimer's disease was reported in *Science* on March 11, 1983. ■



Specific brain changes associated with Alzheimer's disease are visible under the microscope. One of the most prominent neurofibrillary tangles is shown here.
The tangles are pairs of fine nerve fibers twisted around each other and lying in the cell bodies [illegible] neurons. NIH PHOTO 1861

Children with Arthritis: A Research Challenge for the '80s

Sandra D. Levine

Arthritis, a term which encompasses over one hundred different inflammatory disorders of the joints and connective tissues, affects over 35 million people in the United States.

Although these conditions are commonly associated with older adults, approximately 250,000 arthritis sufferers are children. This group of diseases presents difficulties at any age, but for children it means some special problems.

Studies on many aspects of arthritis in children, known collectively as juvenile arthritis (JA), are being conducted under the auspices of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), which has primary responsibility for Federal support of arthritis research, and of several other NIH Institutes.

Juvenile arthritis describes a group of several different conditions, some of which are distinct from the adult forms. About one in every ten thousand children becomes a victim of juvenile arthritis, which consists of a variety of clinical entities distinguished from one another by the joints involved, severity, age of onset, and types of complications.

Juvenile arthritis is characterized by inflammation of the synovium (the lining of the joints) causing swelling, pain, stiffness, heat and often redness of the skin over the affected joint. Movement is painful, but resulting lack of motion may cause stiffness of the joint and muscle weakness. Inflammation over long periods of time can cause damage to the surfaces of the joints. Eventually there may be joint contractures.

Sometimes the disorder affects the rate of growth of involved bones. If the growth centers of many joints are affected, the child's physical development may be slowed. Once the condition is under control, however, normal growth usually resumes.

There are three major types of juvenile arthritis: systemic, pauciarticular and polyarticular, each with its own signs and symptoms.

Systemic JA accounts for about 20 percent of the children with arthritis. It can be found with equal frequency in girls and boys and often begins with a high fever, sometimes accompanied by a rash. Lymph nodes, liver or spleen may also become enlarged. Usually many joints are involved. and inflammation may also be present in the lining of the heart or lungs. Anemia is another manifestation of systemic juvenile arthritis. Joint involvement generally occurs only after the initial presentation of symptoms. Systemic JA usually evolves into poly- or pauciarticular juvenile arthritis.

Pauciarticular JA is the type that affects four joints or less—usually the large joints such as knees, ankles, shoulders or elbows. This form accounts for 30-40 percent of juvenile arthritis patients, and is somewhat more prevalent in girls. However, some boys with pauciarticular juvenile arthritis experience stiffness in the lower back and hips and seem to have a greater predisposition for developing ankylosing spondylitis (a form of arthritis of the spine and hips). Recent research efforts have shown that ankylosing spondylitis, once thought to occur only in adults, also occurs in children.

A complication most often seen in girls with pauciarticular JA, although it can occur in any type, is iridocyclitis (inflammation of the iris and ciliary body of the eye) which affects one in ten children with arthritis. Once it is detected, the condition can usually be treated easily and successfully, but if it is untreated, blindness can result. Since symptoms (redness, pain and diminished vision) do not appear until the inflammation has been present in the eye for some time, regular ophthalmological examinations with a slit lamp are important in juvenile arthritis patients.

Forty to fifty percent of children with arthritis have polyarticular JA, in which five or more joints are involved. Typically these are the small joints of the fingers and wrists, but the weight-bearing joints can also be affected. Unlike pauciarticular juvenile arthritis, the polyarticular form usually results in bilateral involvement, and there may also be low-grade fever. Because it typically affects the small joints as well as the hips, this form more closely resembles the adult forms of arthritis. Polyarticular juvenile arthritis appears to be more prevalent in girls, and typically affects more older children than the other two forms.

One of the major problems with juvenile arthritis is that the signs and symptoms vary so much with each individual and sometimes mimic other conditions, making diagnosis difficult. Unlike arthritis in adults, there is no definitive test for these conditions in children, so they often cannot be diagnosed until other possibilities have been eliminated. Since the symptoms of systemic juvenile arthritis, for example, are fever, rash and enlarged lymph nodes, viral infections such as measles or mumps must be ruled out. Other inflammatory diseases, including systemic lupus erythematosus, psoriasis, rheumatic fever, colitis, and dermatomyositis, must also first be distinguished before a diagnosis of juvenile arthritis can be made. Testing may include blood tests such as rheumatoid factor and antinuclear antibody tests and HLA typing; x-rays of the joints; and joint fluid or tissue testing.

There are no known cures for juvenile arthritis, but it usually can be somewhat controlled with medical and physical therapy. The treatment program depends on the type of juvenile arthritis and the specific symptoms involved, but usually includes medication, rest and exercise. Sometimes heat treatments or splinting may be needed.

Since juvenile arthritis is a multifaceted, chronic condition, many physicians favor a team approach to treatment. There are arthritis clinics and specialized centers where several kinds of health professionals work together to provide total care for the child with arthritis (for example, the University of Missouri Center described in the special arthritis issue of *News & Features,* February 1983, p. 11). Members of the team usually include the pediatrician or family physician; a pediatric rheumatologist; a pediatric nurse specialist; an occupational and/or physical therapist; a medical and/or psychiatric social worker; an ophthalmologist; and an orthopedic specialist if surgery may be needed.

The medications used to treat children with arthritis differ somewhat from those used in adults. This is due in part to the difference in the manifestations of the disease in the two groups. In addition, some drugs are not used in children because of toxicity, fear of long-term effects on reproduction, or possible later development of tumors.

The drug usually tried first is aspirin, which is effective in relieving pain and reducing inflammation and fever in about 75 percent of children with arthritis. However, because fairly high dosages must be taken over long periods of time, therapy must be carefully monitored. Some children receiving aspirin may develop abnormal liver function, and research studies are being conducted in this area.

Other nonsteroidal anti-inflammatory drugs (NSAIDs) are often used in treating adults with arthritis, but currently only a few, like tolmetin, have been approved for use in children.

Another group of drugs, known as disease modifying antirheumatic drugs (DMARDs), are believed to affect the underlying course of arthritis. These drugs are generally used only when the child has been unresponsive to NSAIDs and other forms of therapy for at least six months. Gold-containing compounds are also included in this group and are usually administered only to children with severe polyarticlar juvenile arthritis.

Other types of DMARDs are the antimalarial drugs, which are used very cautiously in children, and penicillamine, which is still considered experimental. Another group of DMARDs, corticosteriods, are used rarely because side effects include softening of the bones and growth retardation. For this reason, joint injections with steroids are generally contraindicated in juvenile arthritis patients. Some NIADDK studies are focusing on determining the safety and effectiveness

These two sisters are meeting the challenge of arthritis head-on. The one on the left, now in her late 20s, has had juvenile arthritis since the seventh grade. She is training to counsel patients in coping with the psychological problems of the disease. Her sister is studying to be a rheumatologist, and they plan to practice together in treating both aspects of arthritis. (Photo courtesy of the Arthritis Foundation.) NIH PHOTO 1862

in JA of drugs that are effective in adults with arthritis. Clinical trials are currently being conducted by a consortium of 15 pediatric rheumatology centers throughout the country that will reevaluate these therapies for use in children.

An important research area for juvenile arthritis is concerned with identifying genetic markers—factors whose presence indicates an inherited predisposition toward the disease, enabling children who are at risk for developing JA to be identified and treated before serious complications occur. Researchers at Brigham Hospital in Boston have found an increased frequency of the marker HLA-DRw5 in children with juvenile arthritis who are prone to iridocyclitis. This indicates that this particular form of JA may be inherited and may help predict which children are at risk of developing eye involvement.

Investigators at Johns Hopkins have found a relationship between another genetic marker—HLA-B27—and a unique form of juvenile arthritis in young women that progresses into spondylitis, which may lead to fusion of the neck vertebrae.

Since juvenile arthritis seems to involve abnormalities of the immune system, studies on rheumatoid factors and immune complexes are being conducted to determine their usefulness as diagnostic determinants. Work is also being done, for example, on antinuclear antibodies as indicators of potential development of iridocyclitis in certain cases and on arthritis in children with the familial form of hypogammaglobulinemia.

Much of the research being conducted on bone disorders is relevant to juvenile arthritis. At Children's Hospital Medical Center in Boston, for example, studies are being done on osteogenesis imperfecta, an inherited disease of the connective tissue which affects young children. Bone fragility and sometimes severe deformity results. Researchers hope that, through recombinant DNA techniques, the gene components that control the synthesis of bone collagen can be spliced together to produce normal collagen and repair damaged bone. Information gained about DNA control of collagen synthesis from these studies may someday be applied to determine whether similar collagen abnormalities exist in juvenile arthritis.

Scoliosis (curvature of the spine) seen in some juvenile arthritis patients, is being studied at Stanford University to see if muscular imbalance causes postural defects, which can be corrected during a child's growth and thus prevent deformity. At the University of California in San Francisco, the CAT scanner is being used to test mineral levels in arthritis patients treated with steroids.

Other studies more specific to juvenile arthritis which are being funded by NIADDK, include research into cellular control of Epstein-Barr (EB) virus in polyarticular JA. Researchers have discovered, in patients with rheumatoid arthritis, a specific defect in the cells that control the production of antibodies to the EB virus, a common virus that causes mononucleosis. This may provide insight into the cause of rheumatoid arthritis and related disorders, such as juvenile arthritis. (See the February 1983 issue of *News and Features*.)

A rapidly developing area of arthritis research is that of artificial joint replacement. Despite the technical problems of implant fixation, loosening, wear and corrosion, this type of treatment can alleviate some of the problems of joint damage in adults. But because children are still growing, replacing their joints presents some unique problems.

At the Robert Brigham Multipurpose Arthritis Center in Boston studies have been conducted on total hip and on total knee replacement in children with arthritis. Seventy prosthetic hips were replaced in 50 children between 1973 and 1981 and 50 prosthetic knees were implanted in 30 children between 1975 and 1981. The major problem for these juvenile arthritis patients before surgery was more often lack of function rather than pain. Studies show that with proper patient selection, most of the bedridden children could walk independently after total hip or total knee replacement. Improvement in the quality of their lives appears to justify the short-term and long-term risks of implant surgery.

Because juvenile arthritis can often involve many years of pain and disability, the emotional burden for the child and the family can be considerable. Children with juvenile arthritis may be physically smaller or sexually less mature than other children, may tire easily, and may not be able to participate in all the activities of their peers. It is very important to their psychological well-being that they be encouraged to lead normal lives, have a positive self image, and not be made to feel "different" from other children. Maximizing the child's development and independence is extremely important.

Therefore, in addition to biomedical research to bring about improved methods of diagnosis and treatment, work is also being done to identify and ameliorate the social, psychological, and other problems unique to children with arthritis. The Arthritis Foundation, for example, is a valuable resource for providing information about medical and other support services that are available in the community. Within the Foundation there is the American Juvenile Arthritis Organization, (AJAO) which has a regular newsletter.

Recently, help for children with arthritis has been accomplished through regional juvenile arthritis centers, which have been established by the Division of Maternal and Child Health, Health Resources and Services Administration. Project objectives include fostering communication among public and private health care providers at national and local levels, and developing a means to evaluate cost and effectiveness of a comprehensive patient care program. Centers have been organized as part of existing pediatric rheumatology programs in, for example, Philadelphia, Houston, and Los Angeles. These pilot programs will test the feasibility of providing vocational and financial counseling, outreach clinics integrated with local health care services and school systems, patient and parent communication networks, professional and patient education, and evaluation systems.

Since juvenile arthritis involves such a complex of diseases with many possible causes and manifestations, the research being conducted by scientists at NIADDK and other NIH Institutes and by extramural grantees all over the country is extensive. This research is supported through investigator-initiated grants and through Multipurpose Arthritis Centers (see the February 1983 issue of *News and Features*).

These researchers are investigating the role of each factor in the etiology of juvenile arthritis to understand and better control its manifestations, to alleviate the pain and disability, and perhaps ultimately one day to be able to cure and prevent arthritis in the thousands of children who will be afflicted by this disease. ■

Teenage Suicide Rates Increase, Now the Third Leading Cause of Death in Young People

Marilyn Sargent

Just 10 days after 14-year-old Viviene wrote about her attempts to strangle herself (an act she had been practicing for months), she was dead, having committed suicide by hanging. Her death was part of an alarming rise in the suicide rate among young people aged 15-25, which has tripled in the last 25 years.

Viviene's writings—letters, diaries, poems—were used to illustrate a method for examining adolescent suicide proposed by Dr. John Mack, Professor of Psychiatry, Harvard Medical School.

Mack spoke at a December meeting in Cambridge, Mass., on "Preventive Aspects of Suicide and Affective Disorders Among Adolescents and Young Adults."

The research planning session was cosponsored by NIMH's Office of Prevention and Center for Studies of Affective Disorders, Division of Extramural Research Programs. It was hosted by the Harvard Programs in Psychiatric Epidemiology and Health Policy.

The meeting's organizer, Dr. Gerald Klerman, former ADAMHA Administrator and new Professor of Psychiatry, Harvard Medical School, and Director of Psychiatric Research, Massachusetts General Hospital, pointed to the timeliness of the workshop.

"Among young people in the 15- to 25-year age bracket, suicide is now the third leading cause of death, following automobile accidents and homicide," said Klerman. "According to the Surgeon General's Report, the death rate has increased for adolescents while mortality rates for all other Americans have gone down."

Contributing factors, according to Klerman, include the state of the economy, demographic fluctuations, and changing family patterns, but he stated, "I believe the opportunities for preventive intervention are promising."

Dr. Stephen Goldston, NIMH Office of Prevention, noted that prevention must be based on knowledge of affective disorders and suicide in young people, but that to understand pathology, normal development also must be understood.

Mack, a Pulitzer Prize winning author, illustrated his system for examining causes of adolescent suicide by using Viviene's words. Through judicious selections from her writings, he showed how her life was affected by each of eight phenomena which must be taken into account to understand suicidal youngsters. These include socio-political forces, biological vulnerability, developmental experiences, and personality structures.

The selections Mack read depicted a sensitive, intelligent girl whose disappointing sexual experiences exacerbated her depression, social isolation, and fragile self-image.

Viviene's writings are marked by a preoccupation with death; the loss of both grandfathers when she was 5 years old seemed to make a lasting impression. She apparently experienced another keen loss during early adolescence when a male teacher, who had given her emotional support, transferred to another school.

Unlike many troubled youngsters, Viviene did not come from a broken home. Nevertheless, she had gained little sustenance from her family and, in fact, felt burdened by a belief that her parents, particularly her mother, needed emotional support from her.

Social isolation, depression, concern with death, and troubled relationships with parents, expressed so poignantly in Viviene's writings, typify the findings reported also by other workshop participants.

For example, Drs. Robert Hirschfeld and Susan Blumenthal, NIMH, found in their review of the scientific literature that poor self-concept, nonsupportive and stressful home situations, illness in the family, and poor coping techniques are associated with depression and suicide in both adolescents and young adults.

The severity of these problems was seen as greatest among those who actually completed their suicide attempts. As the two psychiatrists explained it, depression, suicide attempts, and suicide completions can be viewed as a continuum involving increasingly negative life experiences and inadequate support systems.

Negative personality and psychosocial characteristics were found to be associated also with alcohol and drug abuse by Dr. Gene Smith, Associate Professor, Harvard Medical School. In a 13-year study of 1,521 youngsters, he found that negative traits, such as dependency, immaturity, inconsiderateness, and impulsiveness were predictive of early and continued use of alcohol, cigarettes, and drugs. Further, he reported, substance abuse correlated highly with depression and suicidal thinking.

Another factor which may place adolescents at high risk for depression and suicide is loneliness, more often reported by adolescents than by any other age group, according to Dr. Tim Brennan, Humans Systems Institute, Boulder, Colo., who has been studying adolescent loneliness under an NIMH grant.

Developmental changes, relinquishing bonds with parents, and a growing need for intimacy are among the factors thought to predispose adolescents to loneliness, said Brennan. Also, their marginal status in American society—as neither child nor adult—can foster a sense of non-belonging.

Low self-esteem is strongly correlated with loneliness and may be a two-way street; loneliness may lower self-esteem and/or low esteem may result in behaviors that produce loneliness, Brennan reported.

Loneliness typically emerges between ages 12 and 14, intensifies until 16, and then levels off, he said. Higher levels of loneliness are reported in lower social class youth both at home and in school. Females report more loneliness than males, particularly in the home setting.

Females also report more depression—two to three women for every man, said Dr. Myrna Weissman, Professor of Psychiatry and Epidemiology, Yale University School of Medicine. Noting that depression is strongly related to suicide, she pointed out that many more women than men attempt suicide, although more males succeed because they typically use deadlier methods.

To date, the higher rates of depression in women have not been linked to specific biological causes, Weissman noted. However, evidence that certain forms of depression occur in families suggests a genetic factor.

She discussed a psychosocial theory that may in part explain high levels of depression in women: the "learned helplessness" theory which maintains that females are socialized to become dependent and helpless, two conditions that predispose them to depression. Poverty, high divorce rates, and single parenthood also place many women at risk for depression, she said.

In a report on suicide among American blacks, Drs. Felton Earls and Ada Jamison, Washington University School of Medicine, St. Louis, Mo., noted that during the past 20 years, black and white suicide rates among young people have equalized in contrast with the first half of the century, when black rates were lower.

Socioeconomic conditions appear to play a more influential role in determining rates of suicide, suicide attempts, and depressive symptoms in blacks than in whites, they said.

"If homicide is included with suicide into a single category of 'violent deaths,' then the loss of expected life in young blacks, especially males, becomes alarmingly high." They said that evidence from case histories supports the notion that suicide, homicide, and accidents represent a continuum of "self-destructiveness," particularly in blacks.

Until more is known about emotional development during adolescence, and until clinicians and developmentalists integrate their findings, efforts to prevent adolescent suicide will not be sufficiently informed, said Drs. Anne Petersen and Edward Craighead, Pennsylvania State University.

Petersen and Craighead reported that almost all studies on normal development were done with white males; thus, developmental "norms" may have little application to females or minorities, they pointed out. Also, studies indicate that adolescence is not necessarily a period of emotional turmoil, they said. Empirical evidence shows a gradual increase of moral and ego development during adolescence and young adulthood. Self-esteem usually increases, and "identity begins to stabilize."

However, they noted, contrary to a view based more on wishful thinking than evidence, troubled adolescents do not outgrow their problems but tend to become troubled adults.

Between 10 and 20 percent of the adolescent population experiences enough psychopathology to warrant intervention, they reported. Anxiety and depression (found more in females) and conduct disorders (more in males) are the problems reported most often. Anxiety and depression place individuals at risk for suicide, they reported. Eighty percent of suicides are thought to suffer from depression. Three to five times as many females as males attempt suicide, but three to four times as many males succeed.

In terms of prevention, the investigators suggested that:

- Program developers have a thorough knowledge of developmental, epidemiological, and clinical research in order to know the appropriate intervention targets;
- Programs be multifaceted, dealing with social, cognitive, physiological, and emotional domains;
- Prevention be specific to an adolescent's developmental level; and
- Gender differences be taken into account.

Dr. Julius Richmond, former Assistant Secretary for Health and Surgeon General, chaired the closing session on priority areas for future research. ■

Computer Helps Dentists See Three-Dimensional Images of the Teeth

Hilah Thomas

Dr. Roelf Groenhuis, an NIDR researcher, is using a digital computer to analyze dental radiographs for small changes in periodontal bone.

NIH PHOTO 1863

Dr. Roelf Groenhuis, a Visiting Fellow in the Diagnostic Systems Branch, of the National Institute of Dental Research (NIDR), reported that the use of a computer permits three-dimensional images of the teeth to be produced from as few as eight x-ray images made from different angles.

Each image requires very little radiation so that the total dose to the patient is comparable to that required by conventional methods using one small film packet.

These images appear as successive layers sliced through the tissue so that a dentist can see in three dimensions important clinical details impossible to visualize with conventional x-ray systems.

Dr. Groenhuis and his associates, who have been doing computer simulations of promising alternatives to conventional x-ray systems, also found that the three-dimensional effect was maintained even when the projection angles were restricted to a very narrow range.

Their research shows that an x-ray machine having these capabilities can be made quite small and be relatively simple in design. This work complements other NIDR research being done in collaboration with the National Bureau of Standards, that involves developing a computerized x-ray machine to produce three-dimensional images so rapidly that involuntary movement of the patient between exposures will not influence the results.

The first tomosynthesis, produced in 1935 by a cumbersome mechanical technique, was a laboratory curiosity. About 10 years ago other scientists developed the theory of tomosynthesis. The NIDR researchers based their method on this theory and tested it on a dry human jaw in which they had made an artificial defect. The density of bony tissue has prevented conventional radiographs from revealing many interior details. When knowledgeable dentists studied radiographs of this dry jaw they failed to see much that became clear when they viewed the tomosynthesized images of the same jaw.

The NIDR scientists warn that considerably more research will have to be done before the computerized x-ray machine that they envision can become available for commercial use. ■

Two NIH Institutes Identify the Bacteria that Cause Lyme Disease

Connie Raab Patricia Randall

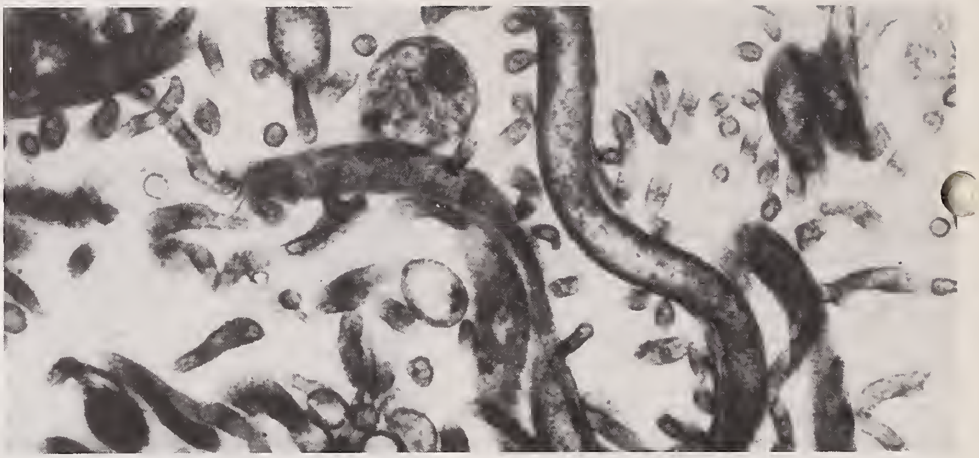
In just a few short years after Lyme disease was first recognized, its cause has been confirmed: spiral-shaped bacteria carried by ticks. Two groups of investigators, including grantees of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) and intramural scientists of the National Institute of Allergy and Infectious Diseases (NIAID), reported their findings in the March 31 *New England Journal of Medicine.* Both groups of investigators isolated bacteria known as spirochetes from patients with Lyme disease. The spirochetes are identical to those previously isolated from ticks by NIAID intramural scientists.

In an editorial in the Journal, Dr. Edward D. Harris, Jr., of Rutgers Medical School, New Jersey, called the investigation of Lyme disease "a triumph" and attributed it to "the inquisitiveness and determination of clinical and laboratory investigators in medicine . . . and a spirit of collaboration among scientists of many disciplines."

In 1975, two mothers in Lyme, Connecticut, alarmed by numerous cases of arthritis in their community alerted the state health department and the Yale University Rheumatology Clinic. With NIADDK support, a team of Yale researchers, led by Drs. Allen Steere and Stephen Malaista, carefully searched for this disease in the Connecticut towns of Old Lyme, Lyme and East Haddam. Within two years they were able to characterize the disorder, first called "Lyme arthritis," which they had found in 39 children and 12 adults in the three villages. The disease has since been discovered in 14 other states, Europe and Australia.

Lyme disease generally begins with a skin rash known as erythema chronicum migrans (ECM), accompanied by fever, headache, and aches and pains. Weeks later, most patients also develop arthritis (joint inflammation); some also develop neurological or cardiac abnormalities. There may be repeated attacks of arthritis, usually in large joints. Still later, some patients develop a chronic destructive arthritis which closely resembles rheumatoid arthritis clinically and histologically (that is, under a microscope).

The geographic and seasonal (late summer) clustering of cases suggested that the disease was caused by some infectious agent. The initial skin rash and the rural setting of the disease suggested it might be borne by an arthropod, such as an insect, mite or tick. One patient recalled being bitten by a tick where the skin rash had appeared. The investigators had no success in testing patients for an immune response (antibodies) to numerous viruses and bacteria.



The causative agent of Lyme disease, *I. Dammini* spirochete in Kelly's medium, is captured here by a scanning electron micrograph. NIH PHOTO 1864

Progress was made, however, when the Yale investigators reported in 1978 that they had identified the tick believed to carry the disease, *Ixodes dammini.*

The Yale investigators next found, in 1980, that the antibiotics penicillin and tetracycline could speed healing of the skin lesion and prevent or reduce the severity of the subsequent arthritis. This finding suggested that some penicillin-susceptible bacteria, such as a spirochete, might be involved.

Indeed, in the summer of 1982, scientists led by Dr. Willy Burgdorfer of NIAID's Rocky Mountain Laboratories, isolated a previously unknown bacterium, a spirochete, from *I. Dammini* ticks collected on Shelter Island, New York, an area known for Lyme disease (see June/July 1982 issue of *News and Features*). In further tests, rabbits injected with this spirochete developed a skin rash similar to that of Lyme disease.

In these most recent articles, scientists have now reported isolating from patients with Lyme disease a spirochete with the same structural and immunologic features as the one found in the ticks. The first group of scientists was headed by Dr. Allen C. Steere of Yale University School of Medicine, whose work is supported by grants from NIADDK, NIAID, the Division of Research Resources (DRR), and the Arthritis Foundation. The Yale investigators examined 142 specimens (from blood, skin lesions, cerebrospinal fluid, lymph nodes and urine) from 56 patients with Lyme disease. The spirochete was recovered from three patients—from the blood of one, the skin lesion of another, and the spinal fluid of the third. The scientists also found antibodies against the spirochete in 90 percent of 40 patients who manifested only the skin rash and in 94 percent of 95 patients who demonstrated further complications. Such antibodies indicated exposure to the spirochete. Not one of 80 control subjects had these antispirochetal antibodies.

The second group of scientists, led by Dr. Jorge L. Benach of the State of New York Department of Health, tested blood samples from 36 patients with symptoms of Lyme disease. They isolated spirochetes from the blood of two of the patients and found antispirochetal antibodies in both. NIAID staff scientists including Drs. Burgdorfer, Alan G. Barbour, Robert Edelman, and Richard Kaslow, contributed to both studies.

The results of these studies indicate that the number of spirochetes to be found in affected tissues is probably small; therefore, isolation of the organism from tissues might provide a low diagnostic yield. The studies did reveal, however, that measuring levels of antibodies that react specifically against the spirochetes may be extremely helpful in establishing an accurate diagnosis of Lyme disease.

Further study of Lyme disease will certainly be necessary, according to researchers. Unlike other infections due to spirochetes, the symptom of Lyme disease which persists over time is generally arthritis. It is not known whether the spirochete is still present in the body at the time the arthritis develops, or whether it sets off in the host a self-perpetuating cycle of inflammation. Writes Dr. Steere, "The issue of whether a persistent infectious agent is necessary for continued disease activity or whether such an agent triggers disease, is of central importance in immune-mediated disorders." Lyme disease, he notes, is similar to many of these disorders, including juvenile rheumatoid arthritis, rheumatoid arthritis, and other chronic types of arthritis.

Dr. Frederic C. McDuffie, Medical Director of the Arthritis Foundation, says that research in Lyme disease is a good example of the progress being made against all forms of arthritis. He says, "Ours is the first generation in which most forms of arthritis can be controlled. With findings such as the one about Lyme disease we are now moving towards causes and cures." ■

Osteoporosis, Bone Fractures in Older Americans, Causes Outlined in New Brochure

Connie Raab

A new pamphlet on osteoporosis, a major bone-thinning disorder affecting millions of Americans, has been published by the Division of Arthritis, Musculoskeletal and Skin Diseases of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK).

Osteoporosis is a condition in which bone tissue decreases, causing the bones to be more susceptible to fracture. Although scientists need to know more about this disorder, evidence suggests that simple changes in lifestyle may prevent, or at least slow down, its development.

Osteoporosis is a major chronic disease, and is the principal underlying cause of bone fractures in older people, especially women. A fall, blow, or lifting action which would not bruise or strain the average person can readily cause bones to break in someone with severe osteoporosis.

An estimated 2 to 5 million Americans seek medical help each year for some problem linked to osteoporosis, and upwards of 15 million Americans have osteoporosis in some degree. The disorder is eight times more common in women than in men, partly because women have less bone mass to start with.

Living bone contains a soft protein framework (the "osteoid matrix") in which calcium salts are deposited. Calcium gives bone its familiar hardness. Bone, like other body tissues, is constantly being rebuilt or "remodeled." Old bone is torn down, resorbed by the body, and replaced with new bone.

As a person gets older, the amount of bone replaced during normal remodeling falls increasingly short of the amount resorbed. By age 35 or 40, both men and women have begun to lose some bone mineral. In addition, by the time a woman reaches her mid-sixties, the body's ability to absorb calcium from food begins to deteriorate, further aggravating net bone loss. Several other factors also contribute to bone breakdown:

- *Menopause* - As a woman ages after menopause, her body's production of sex hormones, including estrogen, declines. Estrogen seems to have a special regulating influence on bone substance. Scientists are not sure of estrogen's exact role, but it is thought to act by slowing down the process of bone destruction. Estrogen also improves the absorption of calcium by the intestine (that is, from food).
- *Too little calcium in the diet* - Many scientists think that a chronic cumulative shortage of calcium intake is one of the most important factors in the development of osteoporosis.
- *Lack of exercise* - Even a moderate amount of exercise helps to stimulate the production of bone tissue.

Today researchers are recommending measures that may prevent, or at least lessen, the effects of osteoporosis. These preventive measures should be undertaken as early as possible. As the pamphlet says, "Osteoporosis is so common that *all* women should consider adopting lifestyle habits that will protect their bones, particularly adequate dietary intake of calcium and regular exercise . . ."

A woman should get plenty of calcium in her diet throughout life, but particularly after age 40. In childhood and adolescence and before menopause, 800 milligrams of calcium a day is probably sufficient. (This is also the recommended daily amount for men.) Pregnant and lactating women require an additional 500 milligrams. After menopause, the requirement for women increases to between 1,000 and 1,500 milligrams per day.

Good dietary sources of calcium include: milk (either whole or skim), solid cheeses such as American or Swiss, and yogurt; fish and shellfish, including oysters, canned sardines, salmon (including the edible bones), scallops and shrimp; and dark green leafy vegetables, such as spinach. Doctors can also recommend calcium supplementation tablets, such as calcium lactate or calcium carbonate, if necessary to bring up the daily intake of calcium.

Staying active also appears to protect against osteoporosis. At this point, scientists have no hard *proof* that regular exercise will prevent the disorder, but there is substantial proof that lack of physical activity hastens bone loss.

People with osteoporosis often have no pain or other symptoms until their bones become so weak that a sudden strain, bump or fall leads to a fracture. Often the condition is first discovered on an x-ray taken for some other purpose.

There are a number of measures to treat osteoporosis. To reduce or stop the rate of bone loss, a physician usually prescribes a diet rich in calcium and adequate in protein (required for tissue building), and usually calcium supplements as well. Vitamin D, which aids absorption, may be recommended as well; vitamin D supplements should only be used under careful physician supervision because vitamin D is potentially toxic.

An effective, and one of the most common, drug treatments currently available for slowing bone loss in women after menopause is estrogen therapy. Estrogen helps preserve bone tissue from further loss, although it cannot strengthen bones already weakened by osteoporosis. Estrogen must be used with caution because recent studies have shown that the hormone, when given as a drug during or after menopause, increases the risk of uterine cancer.

In addition, physicians encourage patients with osteoporosis to remain as physically active as possible.

Scientists around the country, supported by NIADDK, the National Institute on Aging, and other NIH components, are currently studying many aspects of osteoporosis. For example, an NIADDK-supported project at Creighton University is a longitudinal study of 200 women starting at about age 35. Detailed skeletal factors as well as information about total body calcium will establish the profiles of bone change during the pre- and postmenopausal periods. This study and related efforts at the University have established the clinical recommendation of calcium supplementation for osteoporotic patients.

Researchers have found that, unlike established therapies, a combination of sodium fluoride and calcium may actually stimulate an *increase* in bone tissue. Accordingly, NIADDK has initiated a clinical trial to determine the effectiveness of this combination of drugs in reducing the incidence of bone fractures and to identify any side effects. The trial is taking place in two centers, the Mayo Clinic in Rochester, Minnesota, and Henry Ford Hospital in Detroit, Michigan.

A second potential therapy, which may also increase bone volume, was reported recently by investigators at Mayo Clinic and the University of Wisconsin, Madison. Preliminary studies, supported by NIADDK, show that a metabolite of vitamin D, known as 1,25-dyhydroxyvitamin D_3 may have potential for preventing bone fractures in patients with osteoporosis.

Other research studies in osteoporosis range from basic research on the regulation of bone tissue turnover, to studies identifying specific populations at risk, to research projects that identify and evaluate more effective means of treatment and prevention. In that so much new information is emerging about the disorder, NIADDK is planning an NIH Consensus Development Conference on osteopososis for March 1984. The Conference, which will be open to the public and the scientific community, will provide a scientific assessment of current knowledge about osteoporosis. Results of the conference will be broadly disseminated.

Single copies of *Osteoporosis: Cause, Treatment, Prevention* are available free of charge by writing to: Osteoporosis, NIADDK, Building 31, Room 9A04, Bethesda, MD 20205. ■

Several NIH Institutes Involved in Tracking Down Cause of AIDS

Joyce McCarthy

Acquired immune deficiency syndrome (AIDS) was first reported to the Public Health Service in the spring of 1981. By July of that year, NIH had admitted their first AIDS patient to the Clinical Center.

Since that time, NIH has admitted approximately 40 patients, with not more than 3-4 patients in the CC at any one time.

The study, which began last spring, involves scientists from several NIH Institutes (NCI, NIDR, NINCDS, NIAID, NEI, NHLBI, CC) and the Food and Drug Administration.

Their goal is to find the cause of AIDS, describe the disease process, and define appropriate therapies.

Under principal investigator Dr. Henry Masur, Assistant Chief, CC Critical Care Medicine, the researchers will study the neurological, microbiological, pathological, epidemiological and immunological aspects of the disease.

Patients were recruited from the Washington area, Philadelphia, Texas, Florida, and Alabama.

"Overall, there are at least 25 investigators and a dozen laboratories across the NIH campus involved in the study," Dr. Masur said.

Most of the patients in the CC study are homosexual males. There are one to two drug abusers, one hemophiliac, two Haitians, and two women. They include patients with the range of manifestations common to AIDS: those with lymphadenopathy (enlargement of the lymph nodes); those with Kaposi's sarcoma (a rare and agressive skin cancer previously known primarily to affect men over 60 of Mediterranean origin, and kidney transplant patients); and those with opportunistic infections (infections that the victims normally could combat, but cannot fight off because of a collapsed immune system). One patient with Burkitt's lymphoma (a cancer of the lymph glands) has been included.

Homosexuals not affected by AIDS are participating in the study as normal controls.

In the two years that the Centers for Disease Control (CDC) have been tracking the disease, more than 1,200 cases of AIDS have been reported in 34 states and 15 countries. Over 450 persons have died from the ailment and the fatality rate exceeds 60 percent for cases diagnosed before January 1, 1982.

Investigators theorize that there may be a viral agent that attacks the immune system, or an inherent immunologic defect causing the illness.

In this study "some of the control subjects are as immunosuppressed as the affected patients," Dr. Masur said. "All sorts of unusual infections occur in AIDS patients. The primary problem is that their cellular immunity is markedly suppressed and they are predisposed to unusual infections," he added.

The outbreak has spread by sexual contact and probably by blood transfusions. "The epidemiology of the disease is similar to that of hepatitis B," Dr. Masur said. The investigators working with AIDS patients may be at risk for becoming AIDS affected themselves.

Because symptoms early in the course of AIDS are so similar to other diseases, it often goes undiagnosed for weeks or months, during which unsuspecting AIDS victims may transmit the presumed infection to others.

"Patients with pneumonia or meningitis, or a disseminated infection due to agents such as pneumocystis or cryptococcus, candida, toxoplasma, or the tumor, Kaposi's sarcoma, would be considered to have AIDS," Dr. Masur said. However, "No one knows how to identify those at risk for transmitting the agent," he added.

Two other symptoms giving physicians evidence of AIDS are blue or brown spots on the skin, which might indicate Kaposi's sarcoma, or oral thrush (yeast infection in the mouth). Extensive herpes of the mucous membranes might also suggest the disease.

In NIH intramural studies, scientists are exploring several aspects of AIDS:

- At the *NCI Division of Cancer Treatment* investigators are using alpha-lymphoblastoid interferon in combination with chemotherapy to treat Kaposi's sarcoma in AIDS patients. Alpha-lymphoblastoid interferon is one of three types (besides beta and gamma) of interferon and is made from white blood cells.

NCI researchers have also participated in the development of an NIAID study using gamma interferon to treat AIDS patients. In addition, division scientists are examining the possible role of retroviruses in AIDS. Retroviruses are RNA viruses which become incorporated into the genetic material of the cell and are often oncogenic (cancer-causing).

- At the *NCI Laboratory of Pathology*, researchers are examining tissue specimens taken from AIDS patients during surgery to examine the immunological characteristics of certain AIDS-related lymphomas.

- In the *NCI Field Studies and Statistics Program*, scientists are conducting epidemiological studies, looking at immunological profiles of healthy homosexual men in New York, Washington, D.C., and Denmark, and profiles of hemophiliacs without symptoms. In collaboration with laboratories at NIH and elsewhere, they are also conducting studies of individuals with AIDS or members of population groups at risk of develo ing AIDS.

- At the *Division of Virology, Office of Biologics, FDA*, Dr. Gerald Quinnan is studying the significance of cytomegalovirus (one of a group of herpes viruses) infection and cell-mediated (T-cell) immunity.

The FDA studies are aimed at understanding the basis for deficient cytotoxic T-cell responses—why the T-cells malfunction when normally they fight disease by attaching to and destroying foreign materials.

- At *NIDR*, Dr. John J. Hooks is examining the role of viruses and interferon in human immune system disorders. His studies indicate that the AIDS patients examined have abnormalities in their interferon system. These abnormalities are seen as a defect in the ability of the lymphocytes to produce interferon (usually of the gamma type), or as a significant increase in circulating interferon (usually of the alpha type).

- At the *Infectious Diseases Branch of the NINCDS*, Dr. John L. Sever and colleagues are conducting clinical and laboratory research on AIDS. NINCDS is collaborating with the California Regional Primate Research Center on the examination of tissue obtained from rhesus monkeys who have Simian Acquired Immu Deficiency Syndrome (SAIDS)—a disorder which may be similar to AIDS.

They are looking for the presence of new viruses that might be the cause of SAIDS and for known viruses such as cytomegalovirus that can occur in animals with SAIDS.

The NINCDS scientists are also examining the transmissibility of SAIDS by innoculating unaffected rhesus monkeys with tissue obtained from monkeys with SAIDS.

- NIAID's intramural scientists are active in AIDS research. They are searching for an infectious agent (or agents) that might trigger this devastating disease, and conducting any immunologic studies. Several scientists are examining the immunoregulatory defect that occurs in these patients.

In the *Laboratory of Immunoregulation*, Dr. Anthony Fauci and colleagues are evaluating the excessive immunoglobulin production that is seen in contrast to the lack of T-helper cells in patients with AIDS.

(T-cells, produced by the thymus gland, include a class of cells that assist B-cells and other T-cells in their attack on viruses and other invaders. These are called "helper" cells.)

In the *Laboratory of Clinical Investigation,* NIAID scientists are evaluating the role of herpes infections and Epstein-Barr virus in relation to AIDS.

In the *Laboratory of Infectious Diseases,* other scientists are investigating the role of hepatitis in AIDS because virtually all AIDS patients have had hepatitis. NIAID scientists are also evaluating AIDS patients for parvoviruses, a group of DNA viruses.

- At the *NEI Clinical Branch,* Drs. Robert Nussenblatt, Alan Palestine, and Merlyn Rodriques are studying the ocular lesions that occur in patients with AIDS. These studies have a dual purpose: to determine whether there are distinctive ocular signs that might aid in recognizing AIDS victims, and to obtain new clues about the role of the immune system in eye disease.
- NHLBI scientists are also working with the Clinical Center's Dr. Harvey Alter in examing plasma specimens in attempts to transfer a causative agent(s) taken from AIDS patients (hospitalized in the CC) to chimpanzees. The goal is to isolate a transmissible, infectious agent.

Dr. Abe Macher of the CC's Clinical Pathology Department coordinates the complex laboratory analyses required for the clinical workups of AIDS patients, Dr. Macher has diagnosed several unusual disorders now recognized as part of AIDS.

In another treatment attempt, a bone marrow transplant between twin brothers is being performed by NCI scientists. One twin is a healthy heterosexual, the other an AIDS-affected homosexual.

AIDS poses a considerable challenge to the NIH laboratory staff who are faced with the formidable task of examining numerous chemical, hematologic, and microbiologic findings based on extensive workups on AIDS patients.

All these findings are pieces of the AIDS mosaic, and the picture is just beginning to form. Much more extensive research is required to isolate the etiologic agent and develop treatment modes.

"NIH is a good medical center to study this kind of infectious and immunosuppressive disease problem," Dr. Masur said. "This is one of the few places in the country where you can get such a gathering of scientific experts and research facilities in the same place." ■

NIMH Grantees Find that Kidney Dialysis Does Not Help Schizophrenia Patients

Judy Folkenberg

Kidney dialysis is useless as a treatment for schizophrenia, according to a study conducted by a research team at the University of Maryland School of Medicine, and reported in the March 24 *New England Journal of Medicine.*

At a press conference held at the Baltimore campus, NIMH grantee Dr. William T. Carpenter, Jr., Director of the Maryland Psychiatric Research Center, and others, refuted the findings of previous researchers who held that kidney or hemodialysis dramatically improved the mental condition of schizophrenics.

The most widely known reports of the therapeutic value of dialysis for schizophrenia came from Drs. Wagemaker and Cade at the Universities of Louisville and Florida, who said that schizophrenic patients improved substantially almost to the point of recovery in dialysis treatment.

"It is important to evaluate these findings carefully because positive findings raise hopes for many people and also raise questions of policy about the implications of treating great numbers of people with an expensive, time-consuming and even somewhat risky procedure like kidney dialysis," said Carpenter.

Kidney or hemodialysis is a process normally used for patients with renal failure and involves hooking the patient up to a machine for a number of hours where the blood is filtered and impurities removed.

Under double-blind experimental conditions, 15 schizophrenic patients underwent 16 six-hour sessions of renal dialysis and 16 sessions of sham dialysis. Neither the attending physician nor the patient knew whether the bogus or real dialysis treatment was being given.

"By introducing the double-blind method into the evaluation," explained Carpenter, "We could isolate the key issue in dialysis and schizophrenia: what effect, if any, does the blood-filtering process itself have on schizophrenia."

"We found no difference in responses," Carpenter said. "Four patients were somewhat improved after renal dialysis and four were somewhat improved after the sham treatment. Two improved under both conditions. The rest showed no effect from either the renal or sham procedure."

The patients' commitment to the research study was truly impressive, according to Carpenter. Each patient required a minor surgical procedure in the forearm in order to create the bloodflow channels necessary for dialysis. They then underwent 32 six-hour sessions of dialysis over a period of 16 weeks. Carpenter commented that given this kind of patient commitment "it was not surprising to find some changes in the condition of a few because of the placebo or Hawthorne effects."

A placebo effect occurs when the patients get better even though they are receiving the sham treatment, but think they are receiving the beneficial treatment. The Hawthorne effect occurs when the patient improves in response to close, caring attention in a supportive environment.

"While we cannot exclude the possibility that dialysis may help an occasional schizophrenic patient, we have little reason to expect such and can firmly conclude that hemodialysis will not effectively treat most schizophrenic patients," concludes Carpenter.

Dr. Nina Schooler, Assistant Chief, Pharmacologic and Somatic Treatments Research Branch, praised Carpenter's research and said, "The study was exceedingly well designed and well carried out so that both the research and clinical communities can have confidence in the results." ■

MEDICAL CAPSULES

Sandra D. Levine

- According to the National Institute of Allergy and Infectious Diseases (NIAID), recent studies show that patients with Crohn's disease (chronic inflammatory disease of the intestine) have increased numbers of suppressor T-cells (immunoregulatory cells) circulating in their blood, but that suppressor T-cell activity is lacking in the intestinal mucosa. The failure of these cells to localize there as they would in individuals with normal G.I. function results in an abnormal immune response.

This type of disturbance in the immunoregulatory system offers one theory of the pathogenesis of Crohn's disease.

- NIAID is conducting research on primary biliary cirrhosis (PBC), an uncommon chronic disease of unknown origin in which there is inflammation and destruction of bile ducts in the liver. PBC appears to involve abnormalities of lymphocyte function, altering the mechanisms which control inflammatory responses.

Ninety percent of the patients are women, usually in middle age. There is no effective treatment and average survival is about ten years. Liver transplants have been carried out successfully in small numbers of patients, but the disease can recur in the new liver.

Further studies on PBC will focus on understanding more about the way in which lymphocytes control inflammation, and finding anti-inflammatory agents effective in treating this disease.

- Intramural scientists at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) are evaluating several types of therapy for chronic type B viral hepatitis which affects about five percent of the world's population, and is probably the single major cause of cirrhosis and liver cell carcinoma.

One potential treatment being investigated is with interferon, which blocks the virus infection of cells. Initial results were promising, but further long-term studies are needed in order to make an adequate evaluation.

Clinical trials are also being conducted with the anti-viral agent adenine arabinoside monophosphate (Ara-AMP).

It was found that some patients who had been taking corticosteroids and were then withdrawn from these drugs in preparation for receiving anti-viral therapy, exhibited spontaneous improvement. Apparently the corticosteroids caused immunosuppression and withdrawal induced a heightened response of the immune system, clearing the virus. Clinical trials are therefore now underway to test this phenomenon.

- NIADDK reports that ranitidine, a new histamine H_2-receptor antagonist, has been successful in controlling gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. The hypersecretion characteristic of this condition causes severe recurrent peptic ulceration.

The antisecretory agent, cimetidine, has been very effective in patients with Zollinger-Ellison syndrome, enabling gastrectomy to be avoided. However, some side effects such as temporary impotence or breast changes have been noticed in some males who were taking high doses of cimetidine.

Studies indicate that ranitidine effectively controls the gastric acid hypersecretion without these effects.

- The National Heart, Lung and Blood Institute (NHLBI) has awarded a three-year grant to the University of Medicine and Dentistry of New Jersey to determine whether mild hypertension (diastolic level of between 90 and 104) can be reduced without medication.

Three hundred participants aged 21 to 69 will be randomly assigned to one of four programs in this Hypertension Intervention Trial (HIT) using: low sodium and weight loss techniques; behavioral (primarily relaxation) techniques; a combination of these dietary and behavioral regimens; or medication alone (as a control group).

It is estimated that hypertension, the "silent killer" if left untreated, may affect as many as 60 million people in this country.

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

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National Institutes of Health
Building 31, Rm. 2B-10
Bethesda, Maryland 20205

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May 1983

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Exercise May Slow the Physical Decline that Comes With the Aging Process **p. 8**

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Aging: A Special Issue

Story on Page 12

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

News&Features from NIH

May 1983

The concept of the teaching nursing home is being developed to study the long-term medical needs of the elderly both in the community and in nursing homes.

NIA has an active interest in increasing knowledge of chronic diseases and their effects on the elderly, and recently awarded two teaching nursing home grants. Investigators in Philadelphia and New York will study osteoarthritis, senile dementia, accidental falling, chronic infections, and other problems not normally seen in acute care hospitals. See page 14

Regular exercise may have a beneficial effect on the cardiovascular system, help control body fat and increase glucose tolerance, thus helping to slow the physical decline that occurs with aging.

Researchers in St. Louis are looking at the effects of exercise on longevity, body composition, blood sugar levels, skeletal muscles, connective tissue, and cholesterol levels in rats. These preliminary studies seem to indicate that exercise may affect longevity. See page 8

Studies are now underway on the normal age-related changes in visual capacity and the mechanisms that bring these about. The subtle changes in vision that occur during aging include: difficulty seeing objects in low light, discerning fine detail on moving objects, and adjusting to sudden change in lighting conditions.

It is important to understand how and why these kinds of visual impairments come about over time in order to prevent or correct them. See page 6

Unless otherwise indicated, photos are courtesy of the National Institute on Aging.

Behavioral training can help control high blood pressure, according to studies using three behavioral techniques for patients with borderline hypertension.

Patients who measured their own blood pressures several times a day for a month, reduced their blood pressures. Muscle relaxation training and biofeedback techniques enabled them to further reduce blood pressure, especially when these methods were used in combination rather than alone.

Now the effectiveness of behavioral techniques will be tested in patients with more severe hypertension. See page 3

Studies are showing that, contrary to popular belief, retirees experience no more decline in their health than their contemporaries who continue working. This research has found that retirement has a minimal effect on both physical and mental well-being. See page 12

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Editorial Staff

Susan Gerhold
Acting Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

NIH News Branch
Building 31, Room 2B-10
Bethesda, Maryland 20205

Phone:
(301) 496-2535

Introduction: *News and Features* Salutes the Elderly, May is Dedicated to Older Americans

Marian Emr

Since the turn of the century, advances in medical sciences have contributed to a longer life expectancy for most Americans. But although people are living longer, they are not necessarily healthier. The rates of such conditions as heart disease, cancer, hypertension, visual and hearing impairments are increasing in middle and old age; senile dementia is becoming more prevalent as a greater number of people live to ages of high risk.

The purpose of research on aging is to find out why and at what point the systems that protect the body and control body functions begin to break down, making the body vulnerable to chronic debilitating diseases. Poor health is not necessarily a normal consequence of old age. Still, there is a lot to be learned about aging, disease, and the roles of lifestyle and environment before medical science can hope to guarantee a healthy, independent old age for everyone.

This special issue of *News & Features* takes a brief look at the questions and issues being addressed by researchers in aging. What happens over time to the human body and why? What can a person do to stay healthy, longer? Is it possible to characterize individuals who will age "successfully" and to distinguish them from those who will not? How can we separate the myths and stereotypes linked to aging—by the general public, health professionals and scientists, alike—from the truths about what a person can expect in old age?

For years, scientists and others have searched for the single common denominator that will explain the effects of aging and the development of disease. Scientists around the country are using different approaches to study one of the long standing theories of aging. Other investigators are exploring more subtle changes that take place—like those in the aging eye—and how these changes can affect everyday life. Still other investigators are looking at debilitating disease. Several studies are focusing on the causes, mechanisms, and possible treatments of senile dementia of the Alzheimer's type.

Given a half century of biomedical, social and behavioral research on aging, a number of investigators are looking at what people can do to stay healthy as long as they live. It seems that regular, moderate exercise may have a beneficial effect on the heart and lungs and reduce the risk of certain coronary diseases; may help keep body fat down and increase the body's glucose tolerance; and in some cases may aid sleep and alleviate depression. Such behavioral techniques as biofeedback and relaxation training are helping some patients successfully lower their blood pressures without drugs.

Research at the National Institute on Aging's (NIA) Gerontology Research Center in Baltimore, Maryland is attempting to identify people at risk of certain chronic diseases that take years to develop. In one fascinating study, researchers are looking at the association between finger and palm prints and the development of breast cancer.

Alan Baron and Michael Perone, research associate, analyze data from their study of performance deficits in older people. This work is being done in the Behavioral Gerontology Laboratory of the University of Wisconsin-Milwaukee Psychology Department. (Photo courtesy of the University of Wisconsin-Milwaukee). NIH PHOTO 1865

Research in the behavioral and social sciences is questioning some of the common myths associated with aging in America. For years, it has been assumed that retirement has an adverse affect on health. Now, researchers are beginning to find that this is just not true, even in the first few years after retirement. Similarly, investigators are finding that there is little truth in the idea that "you can't teach an old dog new tricks". In laboratory experiments, older people are being trained to overcome learning deficits related to reaction time.

Despite the growing respectability of research on aging in this century, gerontologists have had to combat the negative attitudes of their scientific peers about aging and have had to compete against medical science's interest in the diseases of mainstream medicine. To further stimulate the interest of the scientific community and to encourage researchers to study the chronic diseases of aging where they are often found, NIA has developed a new funding mechanism, the Teaching Nursing Home Award.

Interestingly, not all health workers share society's negative attitudes toward aging. Researchers find that those who work most closely with old people in nursing homes tend to have positive attitudes toward aging and the aged.

May is Older Americans Month, a time to celebrate the accomplishments and contemplate the needs of the 26 million Americans over 65. Aging research holds great promise for improving the quality of life for the aged, perhaps by guaranteeing that the years to come will be healthy, enjoyable ones. ■

Behavioral Training Can Help Control High Blood Pressure

Esther Solomon

NIA studies on patients with borderline hypertension show that biofeedback and relaxation techniques can be used successfully to reduce blood pressure. NIH PHOTO 1866

High blood pressure (HBP), or hypertension, is sometimes called the "silent killer" because it usually produces no symptoms. When blood pressure stays high, it can create a strain on the heart and blood vessels, and can lead to stroke, heart disease and kidney failure.

Hypertension affects about 60 million people in the United States. In many cases, hypertension is controlled with drugs, which usually must be continued for life to keep blood pressure at safe levels. These medicines can also cause unwanted side effects. Researchers at the Gerontology Research Center in Baltimore, part of NIA, are showing that behavioral training can be one alternative to drug use for some patients with borderline hypertension.

Drs. Bernard Engel, Michael Glasgow, and Kenneth Gaarder, tested three behavioral techniques: daily self-monitoring of blood pressure, biofeedback (a process in which patients use monitoring devices to get signals or feedback on specific body functions—in this case, blood pressure sounds in the arteries) and relaxation training.

In this study, patients who measured their own blood pressures daily and reviewed the results once a month with a health professional, achieved reductions in blood pressures. Relaxation training and biofeedback lowered blood pressures further.

Blood pressure readings for adults depend on many factors, including age, sex, race, whether the patient is standing or reclining during testing and the level of activity before measurement. A typical normal reading in an average healthy adult as recorded in a doctor's office is about 120 millimeters of mercury (mm. Hg.) of systolic pressure (the force of the heartbeat pushing blood into the vessels) and 80 millimeters of mercury of diastolic pressure (when the heart is at rest between beats).

The NIA study began with 127 volunteers whose average diastolic blood pressures in the doctors' offices were at least 90 mm Hg. Investigators first tested the feasibility of having these people monitor their own blood pressures. The volunteers learned to use sphygmomanometers and monitored their own blood pressures three times a day for one month. Once a week, their blood pressures were measured by a health professional. At the end of the month, each patient reviewed the measurements with one of the investigators.

About half of the patients were receiving no antihypertensive drugs and half were taking diuretics (medications that remove salt from the body and help reduce blood pressure). This stage of the study showed that patients could successfully monitor their own blood pressures and report the results. In addition, these patients achieved significant reductions in blood pressures.

Patients who completed the initial study were assigned to groups for biofeedback or relaxation training or to a control group which continued self-monitoring. Those using biofeedback and relaxation took their pressures before and after practicing the techniques. After three months, half of the patients in each training group learned to use the other technique.

Patients practicing biofeedback learned to inflate and keep the cuff of the sphygmomanometer at about systolic pressure while listening to and trying to inhibit artery sounds. When they succeeded in reducing systolic pressure, the sounds disappeared. They practiced this technique several times daily, especially at the times of day when previous measurements had shown their pressures to be highest, which was generally in the afternoons. Later they learned to recognize body sensations that resulted in lower systolic blood pressure. Eventually they practiced biofeedback without the sphygmomanometer to lower their blood pressures at convenient times, such as during work breaks, while waiting at traffic signals, or standing in line at a store.

Patients using relaxation techniques learned to identify and relax specific muscle groups which were especially tense. This allows blood to flow more freely through the tissues. They also used these techniques when their pressures were likely to be highest. Eventually they learned to recognize the feelings of relaxation which successfully lowered blood pressure and to practice these techniques at convenient times.

Both the biofeedback and relaxation techniques lowered blood pressures significantly as the patients developed their skills. A combination of biofeedback and then relaxation was better than either method used alone. Improvements were noted in patients using diuretics as well as those taking no medications; however, the techniques were most effective for those not on antihypertensive medication.

Follow-up studies showed that these reductions in blood pressure could be maintained for at least 18 months. About one-third of the patients receiving diuretic therapy were asked by physicians to discontinue the medication. They were able to keep their blood pressures down to safe levels throughout a nine-month follow-up period with no medications.

Having shown behavioral methods to be successful with borderline hypertension, the scientists are testing the effectiveness of these techniques on persons who have more severe high blood pressure.

Dr. Engel advises people who might be interested in trying these methods to consult a doctor. "Although these are self-administered techniques, they must be learned from properly trained professionals and the patients should be under professional supervision," says Dr. Engel. "No one should discontinue medication without consulting his or her doctor."

The Biofeedback Society of America keeps a list of clinicians who use behavioral techniques to control hypertension and other conditions in their patients. To obtain the names of clinicians in specific areas of the country or for further information about biofeedback, contact the Biofeedback Society of America, 4301 Owens Street, Wheat Ridge, Colorado 80033. ■

Free Radicals: A Theory of What Causes Aging

Donna Maxwell

The quest for eternal youth, or at least a longer, healthier life goes on. Once it was thought that bathing in the Fountain of Youth would ward off aging. Today we believe that good health practices allow people to remain healthy as they age. However, the desire for a long and healthy life by simply taking a pill or receiving an injection remains.

Although that possibility is still far off, scientists are beginning to study seriously a number of theories of aging which may explain why aging occurs and how its symptoms may be slowed down. There are two basic concepts of aging. The first states that aging is programmed from birth and that our genetic makeup determines how we will age. The second states that aging is the result of a random occurrence of events rather than programming. In other words, the body is bombarded over time by environmental factors which result in cumulative damage.

One theory of aging based on the random occurrence concept involves microscopic chemical fragments in the body dubbed "free radicals." The free radical theory of aging has been the subject of discussion and controversy for several decades. As early as 1954, Denham Harman, then at the University of California, suggested that free radicals could be the common denominator needed to explain the effects of aging and the degenerative diseases which often accompany it. His theory was initially met with some skepticism because it involved both chemistry and biology and experts in both fields questioned its scientific foundations.

Basically, free radicals are highly unstable chemicals found in everyone's body that are thought to develop as a byproduct of metabolic reactions. For food to be metabolized, oxygen must pass through the mitochondria (a chemically active pocket in the cell). Free radicals are the waste products left behind. Although most free radicals automatically leave the body after participating in metabolic reactions, some remain and their activities are controlled by enzymes. The free radical theory of aging suggests that some of these unstable chemicals accumulate and do damage by interfering with the workings of healthy cells. As evidence, some researchers point to the body's accumulation of lipofuscin, or age pigments, an end product of free radical interactions.

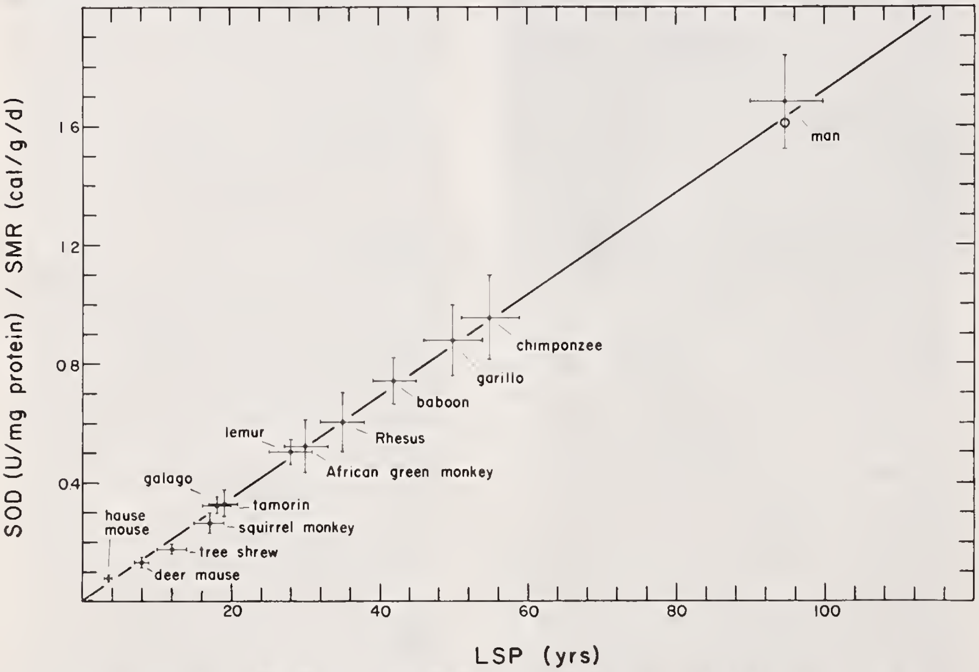
Although the free radical theory is not widely accepted, NIA-supported grantees and scientists are developing new means to study free radicals and to measure the extent, if any, of free radical damage. Some researchers think that free radical damage results in a faulty immune system in later life and thus, degenerative disease. As the body ages there is a decrease in lymphocyte (white blood cells) response to antigens (foreign elements which may spark disease). If free radical damage could be lessened, the immune system might remain stronger. Som researchers now speculate that there may lie the key to a longer, healthier life.

Scientists have found that one of the primary causes of the age-related decline in the immune system is the loss of T-cell function. T-cells are one of two broad classifications of lymphocytes which produce antibodies to fight disease. T-cells are formed in the bone marrow but are eventually housed in the thymus, an organ of the lymph system located at the base of the neck. They take their name, T-cells, from their relationship to the thymus.

One researcher, NIA grantee Margaret Heidrick of the University of Nebraska is studying the free radical theory by measuring the effects of antioxidants (substances thought to inhibit free radical reactions) on the formation and propagation of free radicals. Using a colony of mice, the researchers feed the test substance to the animals in their food, then draw blood to measure and compare the levels of antibodies produced. One test substance, 2-mercaptoethanol (2-ME) was found to result in greater immune functioning at the two times when the animals' immune systems would be least efficient (early life and old age). With the addition of this substance, the average and median lifespans of the mice al increased. This suggests that free radica damage was reduced by the addition of the antioxidant.

NIA grantees, Roy Walford and Richard Weindruch of the University of California in Los Angeles, are also studying ways to lessen free radical damage to the immune system. An important job of the immune system is to survey other cells in the body and destroy those which appear foreign or abnormal. The system has the capability of recognizing "self" (cells or organs or other body parts) and "non-self" (cells of a grafted organ or an abnormal cell). As the system ages, this ability to distinguish between "self" and "non-self" weakens. At times it can even turn on itself, producing autoimmune reactions such as those which result in rheumatoid arthritis. Walford and Weindruch have found that dietary restriction appears to counteract this age-related weakening in mice.

Walford and Weindruch established a feeding regimen that was low in calories but high in nutrition. This type of dietary restriction involves undernutrition not malnutrition. They selected mice that were approaching middle age and had shown signs of a gradually weakening immune system. One group of mice was fed normal amounts of food while other group was fed a limited diet wi periods of fasting. It was found that not



Dr. Richard Cutler of the Gerontology Research Center and Dr. Irwin Fridovich of Duke University are finding that long-lived mammals have higher levels of superoxide dismutase (SOD) than do shorter-lived species. (Photo courtesy of Dr. Cutler). NIH PHOTO 1867 only were the immune systems of the diet-restricted mice revitalized, but also they lived 10 to 20 percent longer than the controls on regular diets.

In terms of potential human application, dietary restriction has many drawbacks. Although it may extend lifespan, it is difficult and possibly dangerous to adhere to the regimen for the long periods of time necessary for it to be effective. Also, researchers must still determine whether or not severe caloric restriction over long periods of time affects mental development or activity. Researchers are often hampered by the length of time needed to measure the success or failure of the regimen on humans—often 70 to 80 years.

Walford and Weindruch's research differs from other studies in that they only restricted the diet of adult mice. In earlier studies by Walford and others, dietary restriction was initiated at the time of weaning. This resulted in stunting the growth of the animals. At this time it remains highly questionable whether any form of dietary restriction is a feasible method for extending human life.

Other investigators, Richard Cutler of the Gerontology Research Center (GRC) and Irwin Fridovich of Duke University, have used different animal species to study the protective effects of superoxide dismutase (SOD) on the immune system. SOD is an antioxidant which may detoxify free radicals and is one of several substances currently being tested as a determinant of longevity. The researchers think that the wide range of maximum lifespan potentials (MLP) of different mammalian species is due to the amount of SOD produced in their bodies.

Cutler speculates that lifespan is regulated by a few longevity determinant genes which are only one small component of a species' total genetic makeup. For example, although chimpanzees are man's closest relatives, they only live half as long as humans. Cutler hypothesizes that this discrepancy is due to the higher efficiency level of human longevity determinant genes and the fact that the human body has nearly twice as much SOD as the chimpanzee's. Although SOD in the form found in health food stores is not beneficial as an antioxidant because it cannot be absorbed by the digestive tract, Cutler believes that other substances currently under study may stimulate the body's natural production of SOD and offer further protection from free radicals. Clearly, more research is needed before we can hope to understand the significance of this work.

Although studies of the theories of aging are still confined to the laboratory, it is likely that eventually the day will arrive when the human lifespan can be extended and technology's answer to the Fountain of Youth may well be available in capsule form. ■

Neurochemical Studies Point Toward Possible Treatments for Dementia

Marian Emr

Senile dementia of the Alzheimer's type (SDAT) is a disease of catastrophic proportions. Now regarded as the major form of old age "senility," it is a surprisingly common disorder that affects the cells of the brain. While experts formerly believed that Alzheimer's disease only occurred in persons under 65, this disorder is now recognized as the most common cause of severe intellectual impairment in older individuals. Whether the classic form of Alzheimer's disease, which was first described in a middle-aged adult, is identical in cause, mechanisms, and course to senile dementia of the Alzheimer's type is a matter of some controversy.

The major debilitating symptoms of SDAT include serious forgetfulness—particularly about recent events—and confusion. At first, the individual experiences only minor and almost imperceptible symptoms that are often attributed to emotional upsets or other physical illnesses. Gradually, however, the person becomes more forgetful and this may be reported by anxious relatives. The person may neglect to turn off the oven, may misplace things, may recheck to see if a task was done, may take longer to complete a chore that was previously routine, or may repeat already answered questions. As the disease progresses, memory loss and such changes in personality, mood, and behavior as confusion, irritability, restlessness, and agitation, are likely to appear. Judgment, concentration, orientation, writing, reading, speech, motor behavior and naming of objects may also be affected. Even when a loving and caring family is available to give support, the victim of SDAT is most likely to spend his or her last days in a nursing home or long-term care institution. At this time, there is no cure.

In a decade marked by major advances in the fields of neuroscience and aging research, scientists have employed a variety of methods to investigate the possible cause(s) of SDAT. Studies have looked at the roles of deleterious changes in brain chemistry, trace metals, and slow-acting viruses, as well as the roles of heredity and of changes in the aging immune system.

Since the mid 1970s, research scientists have been following the lead of the first reports of a significant and progressive decrease in the activity of the enzyme choline acetyltransferase (ChAT) in the brain tissue of SDAT patients. ChAT is a key ingredient in the chemical process which produces acetylcholine, a neurotransmitter involved in both learning and memory. Until recently, the most exciting findings were those which showed a link between this change in neurochemical activity, and changes in both cognition (such as memory loss and disorientation) and the physical appearance of SDAT brains, particularly the number of characteristic plaques (degenerated nerve cell pieces which form around a fibrous core in the cerebral cortex). Current studies are aimed at expanding our understanding of the neurochemistry of human aging and dementia.

While recognizing that SDAT probably involves more than one neurotransmitter, researchers in the basic sciences have attempted to determine what causes the particular decline in ChAT and clinical scientists have attempted to compensate for this deficit as a way of treating the serious symptoms of SDAT.

The first studies in this area involved ingestion of the drug choline chloride, which not only produced some rather unpleasant side effects, but failed to increase acetylcholine production in the brain. Other early studies employed pure forms of lecithin, the dietary source of choline with the same intent of increasing acetylcholine production. Lecithin increased the level of choline in the blood more than choline chloride, continued to have this effect for a longer period of time, and had no serious side effects—but also showed no consistent or marked benefit.

In 1978, research at the Bronx Veterans Administration Hospital suggested that physostigmine, a drug which blocks the otherwise fast breakdown of acetylcholine in the brain, had a positive effect on the memory of elderly Alzheimer patients, but that the dose required to do so varied from subject to subject. Use of the drug, however, was plagued by problems. It was hardly practical for SDAT patients since it had to be given by injection and its effects lasted less than one hour. Now, a research team supported by NIA and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) at the Albert Einstein College of Medicine may have overcome some of the difficulties inherent in the use of this drug. Using an oral form of physostigmine, Leon Thal found marked improvement in six out of eight Alzheimer patients when the drug dose was carefully planned for each individual and given in combination with lecithin. The drug's effect lasted longer than the investigators anticipated so that memory improvement was still noticeable on the morning after the drug was administered. Also, side effects such as nausea and cramps were only apparent when the patient received more than the optimal dose to improve his/her memory. With support from NIA, Thal hopes to expand these studies and to begin work on tetrahydroaminoacridine, a drug which also acts to slow breakdown of acetylcholine but may be safer and more effective than physostigmine. ■

Investigators Study the Aging Eye

Marian Emr

Different people harbor different fears about growing old. Some fear losing their minds. Others fear losing their physical strength. Still others fear losing their beauty. Most of these anxieties associated with old age center on issues related to quality of life or to a person's sense of independence. In this respect, loss of vision should be included among the list. Vision affects our ability to work, to interact socially, and to go where and when we want to go. There is little we do in day-to-day life that is not affected by the ability to see.

Serious visual problems caused by cataracts, glaucoma, senile macular degeneration and other conditions affect no more than four percent of the elderly population. But all older people experience more subtle changes that can affect daily routines. Around age 30 or 40, vision begins to decline. Over the past several years, NIA grantee Robert Sekuler and his colleagues at Northwestern University have attempted to develop a better understanding of the full range of changes which take place in the aging eye.

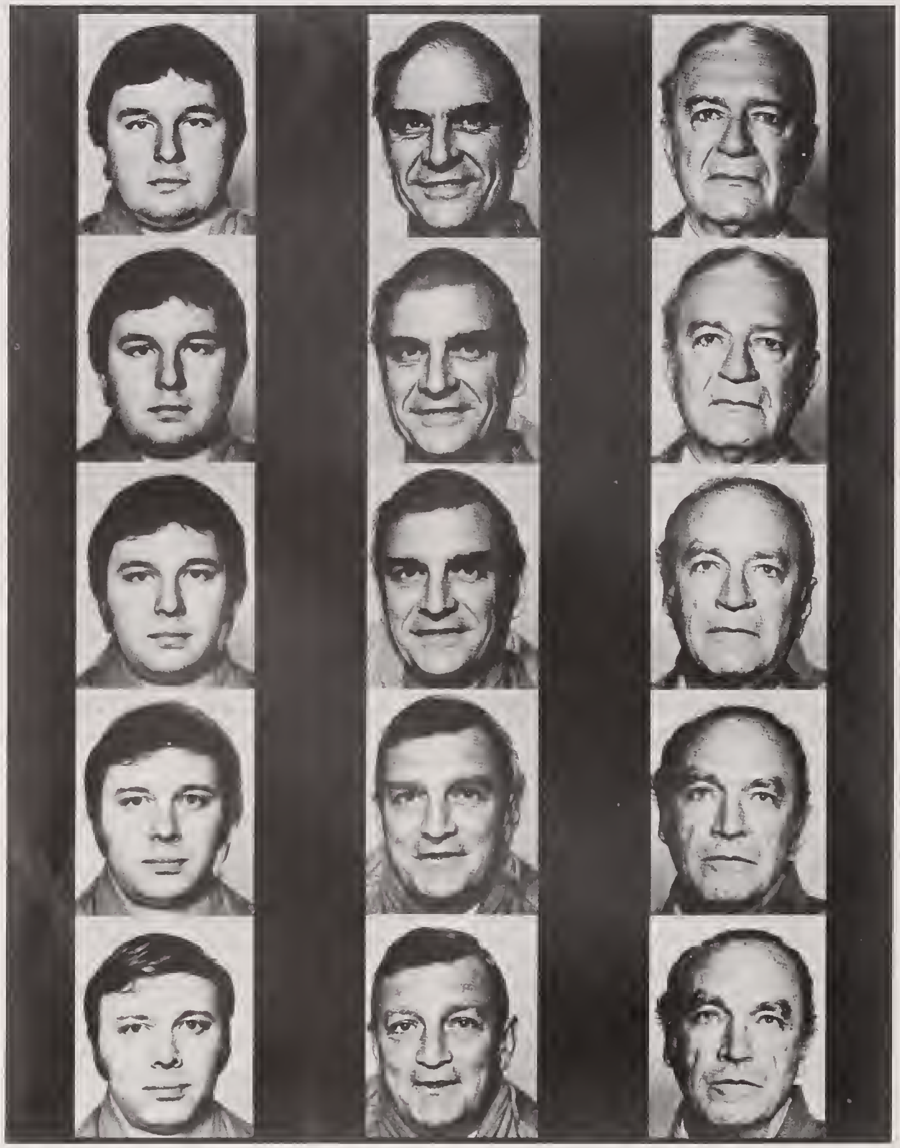
The familiar eye chart used by ophthalmologists and optometrists easily measures loss of visual acuity. It tests vision in terms of the smallest letter which can be read, and provides the practitioner with a means of prescribing corrective lenses or therapy. In general it shows a wide range of capabilities and deficits in people of all ages with regard to the ability to see fine detail. But it also is performed under optimal conditions of high contrast as the subject views a non-moving target. As such, it is a poor test of the demands that will be placed on an individual in most daily activities, with the exception of reading.

Ophthalmologists and optometrists also are able to use the measures available to them to test for presbyopia, a commonplace difficulty older people report in focusing on close objects. This problem develops as the lens of the aging eye loses its ability to change its shape and consequently its ability to bend light. Although medical scientists do not yet understand why this happens with aging, properly prescribed glasses can correct this problem in most cases.

During the past decade, behavioral and biomedical researchers have identified a number of other visual functions which appear to decline with advancing age. Older people seem to have greater difficulty discerning objects under low contrast conditions, seeing fine detail in a moving object, adjusting to glare or sudden darkness, and seeing in low light. One condition which accounts, in part, for some of these problems as well as for changes in acuity, is senile miosis. In order for a person to see, light must penetrate the pupil and pass through the crystalline lens behind the pupil before reaching the retina. Age-related changes in both the pupil and the lens, including the reduction in pupil size known as senile miosis, limit the amount of light reaching the retina. It has been estimated that the retina of an average 60 or 70-year-old person receives only one-third as much light as that of an average 20-year-old.

In order to develop a more complete picture of what happens to our eyes as we age, Robert Sekuler and his colleagu studied older people's ability to s objects of all sizes, not just the small ones they are exposed to in standard eye tests. In one of a series of studies at Northwestern University, Sekuler and his colleagues thus uncovered a previously unsuspected visual handicap: the diminished ability to see intermediate sized as well as small targets.

Using a series of vertical bars produced on a cathode ray tube, the investigators measured the "contrast sensitivity" of a group of young undergraduates as compared to a group of healthy elderly volun-



In order to test visual acuity in a real-life situation, Dr. Robert Sekuler conducted a study involving recognition and identification of faces. In this illustration, the six faces at the top and bottom of each column were those of real people. The other faces in each column were photographic composites for use in the discrimination task. (Photo courtesy of Dr. Robert Sekuler).

NIH PHOTO 1868

rs more than 50 years older. Patterns were composed of alternating light and dark bars. Those with thin bars made up targets with fine structures of high spatial frequency; those with thick bars made up targets which had what the researchers called "coarse" structures of low spatial frequency. Viewing these targets can be roughly compared to looking at small objects as opposed to large objects, or to the small detail of an object as opposed to the gross features of the same object.

The greatest differences between the two age groups were apparent as they viewed targets with intermediate and high spatial frequencies. At some spatial frequencies, older people needed three times as much contrast to see the patterns as clearly as did the younger subjects. Although the investigators had carefully screened their subjects and had excluded persons with eye problems, they used the results of other studies to show that neither cataracts nor glaucoma could have accounted for the differences they found in the two age groups. The investigators also conducted tests to be sure that what they had found was a genuine age-related reduction in vision and not simply a reluctance on the part of the older subjects to say what they had seen. Thus, Sekuler concluded that the greatest rformance differences between a group of healthy young adults and a group of healthy elderly adults are in the ability to see intermediate and small objects. Sekuler's original findings were in a group of 25 young subjects and 10 elderly subjects. He has since replicated his earlier findings in a group of 100 adults, the majority of whom were over 60 years old.

It is important to emphasize that some of these differences would not have been detected on standard eye examinations, although the state of the art has improved in recent years. A number of optometrists, ophthalmologists and neurologists now routinely include simple techniques for measuring contrast sensitivity as part of their examinations of elderly clients.

Problems with seeing large objects, or the gross features of an object, might make it difficult to distinguish a figure from its background or to recognize a familiar face; it might even affect an older person's balance and coordination. In order to test his findings in a real-life social situation, Sekuler next conducted a study involving the recognition and identification of faces.

Sekuler and his colleague, Cynthia J. Owsley, now at the University of Alabama, ked subjects to view a series of slides which pictured the life-sized faces of some 50 middle-aged men. None of the men had facial hair, glasses or any other obvious feature which might easily distinguish him from any other. Again, two age groups were tested. Healthy young subjects who averaged 20 years of age were compared to healthy older subjects who averaged 74 years of age. All subjects had good visual acuity under high contrast conditions. In fact, there were only small differences in acuity between the two age groups.

Each subject was asked to complete two sets of tasks. In one set, subjects viewed one face at a time, but when it was first projected on the screen, there was little or no contrast. Subjects could adjust the contrast until they were able to detect something on the screen, usually nothing more than the outline of a face. They then moved on to the next slide.

In a test of discrimination, Sekuler and Owsley projected 16 slides picturing the faces of two men side by side. In some cases, the faces were identical; in other cases, they were not. Once again, when the slides were first projected there was little or no contrast. Subjects were allowed to adjust the contrast until they were able to determine if they were looking at one man or two. At all ages, subjects required a greater degree of contrast to discriminate between two faces than they did to detect a single face. However, in both tests of detection and discrimination, older subjects needed twice as much contrast as did their younger counterparts in order to complete the task.

Many routine activities are performed under low contrast conditions. One notable example is driving in the rain or fog. Sekuler's work—first in studying patterns in lines and then discriminating faces—shows that under low contrast conditions, older persons might be placed at a special disadvantage. Such conditions call upon an individual's ability to detect an object's gross features rather than small detail. Thus, some older persons may be severely handicapped, regardless of how well they read street signs or demonstrate their visual acuity in a regulated environment.

In their most recent work, Sekuler and his colleagues are studying the role of contrast sensitivity in an older person's ability to detect moving targets. As part of their earlier work with vertical bars, the investigators selected 8 older and 25 younger subjects and tested their sensitivity to bars which drifted across the screen. As expected, the older subjects were less sensitive to the moving bar. The faster the bar moved, the more difficult it became to detect it. According to Sekuler, this design allows for a methodical study of the movement sensitivity that has been reported by other researchers working with elderly subjects. Already, Sekuler has expanded this study to include a group of 100 subjects. In future studies, the investigators hope to further quantify this sensitivity to moving objects, and perhaps to understand better its impact on the lives of older persons.

Although Sekuler and his colleagues speculate that the visual impairments they have observed may be the result of the normal aging process, they insist that their findings cannot be used to arbitrarily define the capabilities—or limitations—of older persons. In fact, the investigators are quick to point out that some of the changes they have found in the aging eye might be subject to individual differences, although perhaps not to the same extent as changes in visual acuity are subject to individual differences.

Although medical science has given a great deal of attention to the diseases of the eye—many of which take their greatest toll among the aged—little attention has been given to the study of normal age-related changes. There is a great need to understand further these changes and the mechanisms which cause them, to devise tests which can accurately measure these changes, and to study their effects for daily living on such complex behavioral tasks as driving and even walking. With improved detection of any problems that occur, it may be possible one day to correct or prevent these problems. ■

Studies Pinpoint Beneficial Effects of Exercise

Mary Anne Kurz

Along with public interest in physical fitness, there is much research interest in long-term exercise as a possible means to prevent or alleviate some of the diseases and disabilities of old age. It is not yet clear whether exercise, carried out on a regular basis, will affect the process of aging itself. Nevertheless, some scientists believe that exercise can lead to a slowing of the age-related physical decline brought on by certain diseases and lifestyles.

One such investigator is John O. Holloszy at Washington University in St. Louis. Holloszy believes that participation in a regular, moderate exercise program may have a beneficial effect on the heart and lungs, help keep body fat down, increase glucose (sugar) tolerance, reduce the risk of coronary artery disease, and in some cases aid sleep and alleviate depression.

Holloszy's studies of exercise, which are supported by a research grant from NIA, have corroborated some earlier findings about exercise and yielded important insights into certain aging processes.

Holloszy is evaluating the effects of long-term, regularly performed exercise on longevity in the rat. He wants to determine which types of illness are more common in sedentary rats, and if causes of death differ in active and inactive animals. He is finding that a lifetime program of moderate exercise can prolong rats' lives. But more research must be done before any conclusions can be drawn about types of illness and causes of death in exercising versus sedentary animals.

The subjects of Holloszy's study are 440 male Long Evans rats. The animals were assigned to four different groups. Those in the first group exercised regularly on activity wheels attached to their cages or by swimming for four hours five days a week. These animals either ate freely or were given almost as much food as they normally would eat. (Some restriction was required to keep the animals exercising voluntarily.) The other three groups of rats got no exercise. One group was given as much food as the exercisers. Another group ate as much food as they wanted. And a third group was diet-restricted to keep their weight the same as that of the exercisers. Some of the rats in each group were studied at different ages to determine the effects of their diet and exercise regimens; others were studied after they died in old age.

Although the study is not finished, early results show that exercising rats live longer than inactive ones. About half the runners were still alive at 34 months of age, compared to 30 percent of the sedentary animals that ate as much food as the runners and 25 percent of the freely eating inactive animals. The rats that lived the longest, however, were those whose diets were restricted so that their weights matched those of the exercising animals. These rats were given 65 to 70 percent of the food they normally would have eaten. It is known that severe food restriction increases the lifespan of rats, but why this happens is not fully understood.

Holloszy and his associates also are looking at the effects of aging and exercise on body composition, blood sugar levels, skeletal musles, connective tissue, and cholesterol levels.

Their studies have reconfirmed the fact that there is a progressive change in body composition with age. In rats, as in humans, there is a gradual loss of lean body tissue and an increase in body fat with age. Holloszy's results showed, however, that lean tissue declines at a slower rate in rats that exercise. Furthermore, exercise may be more effective than dietary restriction in controlling body fat in older animals. Rats living on restricted diets and not exercising had more body fat than exercised rats given plenty of food.

Another finding by Holloszy is that the number of fat cells increases in older rats. This is contrary to reports by other scientists that fat cell number is fixed early in life. In this study, the number of fat cells was highest at 28 months (late life for a rat).

Holloszy also compared sensitivity to insulin and the rate at which skeletal muscles take up glucose in young and old rats. Insulin is the hormone that enables the body to use glucose properly. Holloszy found that the rate at which skeletal muscles take up glucose was not significantly different in 24-month-old rats than in 9-month-old ones, providing evidence that insulin sensitivity need not deteriorate with age. Then he compared glucose uptake in freely eating rats that exercised, freely eating rats that were sedentary, and sedentary rats whose diets were controlled so that their weight was the sam[illegible] as that of the exercisers. He found th[illegible] glucose uptake by skeletal muscle was significantly higher in the exercisers than

Kevin Gorman, physician's assistant (left) and Joel Posner, M.D. (right) test an elderly subject's pulmonary function during exercise. Dr. Posner is principal investigator of the Philadelphia consortium's exercise capacity research project. Mr. Gorman is the administrative director of the project. (Photo courtesy of the Philadelphia Geriatric Center).

NIH PHOTO 1869

in the sedentary freely eating rats, but not in the diet-controlled sedentary rats. Thus, both exercise and weight play important roles in the body's ability to handle sugar.

Glucose (sugar) uptake by fat cells and their sensitivity to insulin also were studied. Holloszy found that the fat cells of the freely eating sedentary rats were large and extremely resistant to insulin. In contrast, the fat cells of the exercisers were small and highly sensitive to insulin. The fat cells of the diet-restricted sedentary rats were intermediate in size and sensitivity to insulin. Because the fat cells of exercising animals are very insulin sensitive and have a greatly increased ability to take up and oxidize glucose, they are able to store energy rapidly during the recovery periods between bouts of exercise.

The results again showed that age was not a factor in fat cell sensitivity to insulin. Rather, the sensitivity varied according to the size of the fat cells, which appeared to be influenced by exercise. Interestingly, the study also found that fat cells of the 24-month-old exercisers were as small as those of the 9-month-exercisers, even though the former engaged in only one-fourth as much activity.

In another approach, Holloszy measured the animals' responses to a glucose tolerance test similar to that used in diagnosing human diabetes. Preliminary results indicate that only minor changes occur with age in the response to this test. But, again, the beneficial effect of exercise was apparent. Animals that exercised responded to the test better than inactive ones did.

If these findings can be applied to humans, they suggest that exercise may help control weight and possibly protect against adult-onset diabetes, which can be triggered by obesity in individuals who are genetically predisposed to this disorder.

Examination of the rats' skeletal muscles revealed only relatively minor changes in biochemical and physiological function with normal aging. One such change is that muscles contract more slowly. In contrast to reports by other investigators, Holloszy's results showed no deterioration with age in the muscles' ability to use oxygen.

The effects of aging and exercise on connective tissue, ligaments and tendons in particular, also were analyzed. The investigators found a decrease with age in the proteoglycan (glycoprotein) content of the Achilles' tendon and the patellar ligament attached to the knee. Proteoglycans are thought to play an important role in maintaining connective tissue elasticity. Older rats that exercised, however, showed evidence of maintaining greater elasticity than sedentary ones.

This rat, who is running in an exercise wheel, may live longer than his sedentary litter mates. Studies by NIA grantee John Holloszy at Washington University in St. Louis suggests that a lifetime program of moderate exercise can prolong rats' lives.

NIH PHOTO 1870

Cholesterol levels, too, were strongly affected by exercise in this study, a finding which supports other research in this field. The older inactive rats had significantly higher plasma cholesterol levels than did the younger sedentary animals. But exercise protected against the increase in cholesterol with age. The older swimmers' cholesterol levels were markedly lower than those of the freely eating sedentary controls, and the ratio of HDL cholesterol (the type that protects against heart disease) to total cholesterol was significantly higher. Food restriction partially protected against the increase in cholesterol with age. The older weight-controlled rats had lower cholesterol levels than did the freely eating animals. But the swimmers had the lowest levels of all.

Holloszy and his associates also are investigating exercise in humans. In one study, they compared the physiology of older athletes who were active in age group competition with that of younger atheletes and untrained men. Despite the inevitable decrease in heart rate and maximum oxygen uptake capacity ($VO_{2\,max}$, a good indicator of cardiovascular respiratory function) with age, they found that some men in their sixties and seventies are able, by means of exercise training, to maintain their $VO_{2\,max}$ levels above those of healthy untrained young men.

The researchers also are evaluating exercise training in patients with coronary artery disease. One study found that training, if sufficiently intense and prolonged, can significantly reduce myocardial ischemia, the deficiency of blood supply to the heart muscle caused by obstruction of the coronary arteries. Another study found that exercise training improved maximum oxygen uptake capacity, heart rate, and performance of the left ventricle of the heart in coronary patients.

A 5- to 10-year longitudinal study of athletes aged 50 and above who are participating in age group competition is currently underway.

Although the answers are not all in about the possible long-term health benefits of regular exercise, especially for previously inactive middle-aged and older individuals, Holloszy recommends some form of regular physical activity for most people. The exercise program, of course, must be tailored to the individual's capabilities and needs. Jogging is not for everyone—disorders such as arthritis and minor skeletal abnormalities, in fact, preclude this type of exercise for many people. But there are numerous other forms of exercise. Walking, flexibility exercises, and swimming are probably best for most older people.

While exercise may not affect aging itself, it does help protect against many of the diseases that shorten life. According to Holloszy, "Exercise has a beneficial effect against all the major killers except cancer." ■

Fingerprints Help Analyze and May Predict Several Diseases

Esther Solomon

For centuries, people have looked for messages in palm and finger patterns. Determined before birth, these patterns are unique for every individual, even identical twins, and have served as an important means of personal identification.

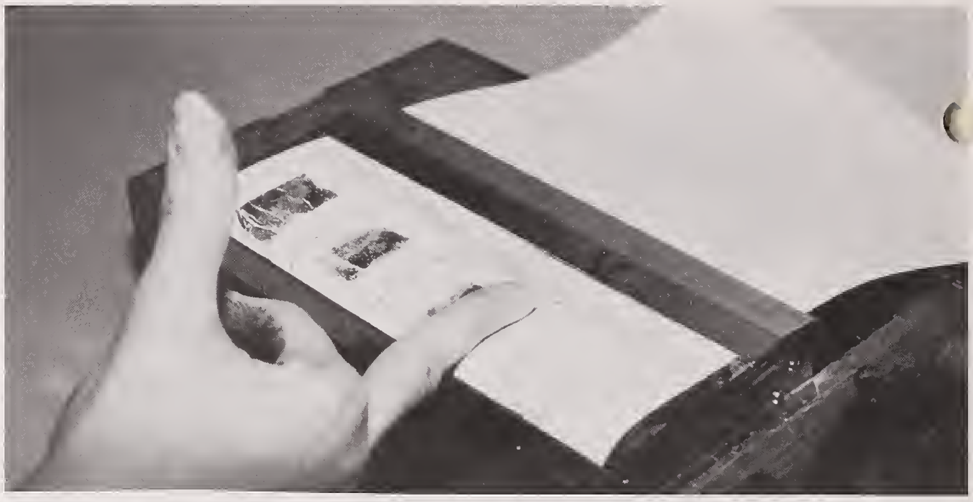
In 1939, a scientist named Harold Cummins noticed that a high proportion of Down's syndrome patients have certain characteristic finger and palm print patterns. Since then, other scientists, including Dr. Chris C. Plato, a geneticist at NIA's Gerontology Research Center (GRC) in Baltimore, have focused on the relationship of finger and palm prints (known as dermatoglyphics) to some birth defects and diseases. As they study the processes of aging over the adult lifetime, these scientists are exploring ways that dermatoglyphics can be useful in the diagnosis of the diseases associated with aging as well as other diseases.

Dr. Plato oversees a collection of finger and palm prints from over 200 different human populations and disease groups. The prints come from such diverse groups as Pacific Islanders in Micronesia to Indian natives in the South American Andes. Some prints are from individuals exposed to chemicals or drugs before birth, such as children of the Love Canal area. Others are from victims of such diseases as cancer or Down's syndrome.

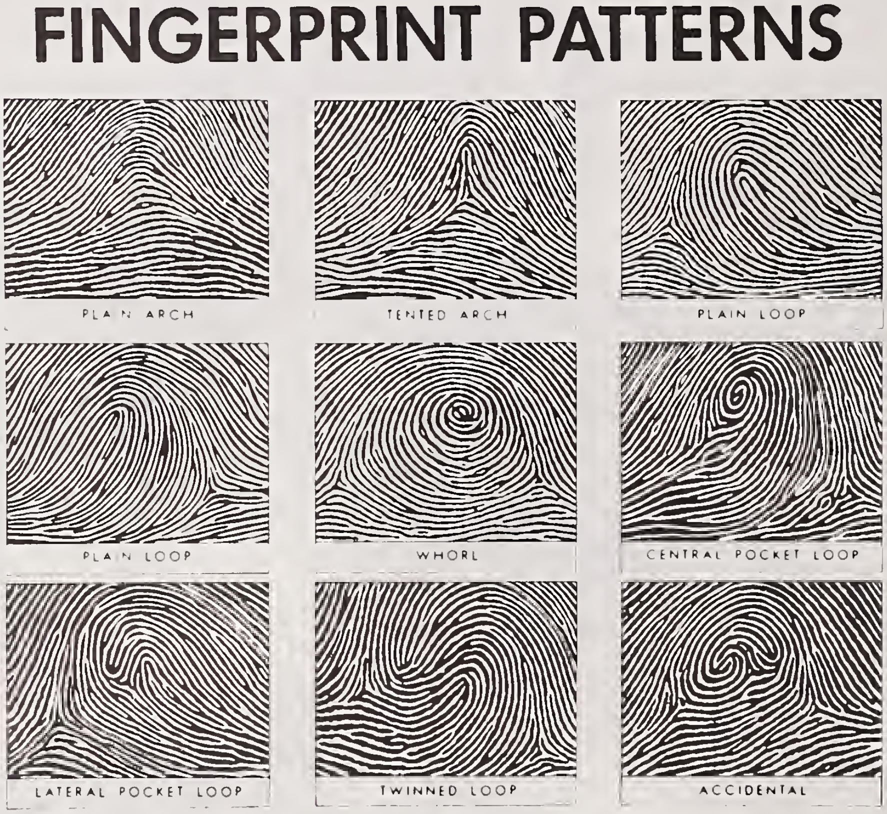
Fingerprints are analyzed by noting the numbers, locations and other characteristics of fingertip patterns, called whorls, loops and arches. Each of these patterns is composed of ridges. Whorls, for example, are made up of concentric ridges. The points at which three ridges converge are called triradii.

On the palm, the direction of the ridges, the numbers and locations of triradii and the variations in the creases are excellent genetic and developmental markers in studying birth defects and other conditions.

Finger and palm dermatoglyphics vary by sex, age and racial group. Both environmental and genetic factors influence dermatoglyphic patterns during the first trimester of pregnancy, after which the patterns do not change throughout life. No two individuals have the same prints. Even though identical twins have very similar patterns, variations are caused by the fetus' position in the uterus and perhaps by differences in the blood supply and other factors. Rubella (German measles), genetic defects and certain drugs can also influence dermatoglyphics.



Scientists at NIA's Gerontology Research Center are exploring ways that fingerprints (dermatoglyphics) can be useful in the diagnosis of diseases associated with aging as well as other diseases.
NIH PHOTO 1871



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NIH PHOTO 1872

Dr. Plato and his colleagues, Drs. Ralph M. Garruto and D. C. Gajdusek from the National Institute of Neurological and Communicative Disorders and Stroke, and Dr. Wladimir Wertelecki from the University of South Alabama School of Medicine, are investigating how exposure to chemicals and other environmental and genetic factors may affect dermatoglyphic traits. In collaboration with other laboratories, the investigators are analyzing prints from children exposed to the chemicals at Love Canal since before birth and are comparing them to prints from children of other areas. To avoid bias, each print is coded so that the person analyzing it does not know whether it is from a child exposed to chemicals at Love Canal or from another chosen for comparison.

At GRC, Dr. Plato and his associates are particularly interested in possible association between dermatoglyphics and normal aging processes as well as diseases of the middle and later years. They are studying dermatoglyphics in patients with osteoporosis, osteoarthritis, amyotrophic lateral sclerosis, Parkinsonism dementia, breast cancer and other diseases, and comparing them with the dermatoglyphics of non-affected individuals.

In collaboration with scientists from the University of Medicine and Dentistry of New Jersey and the St. Barnabus Medical

Center in New Jersey, Dr. Plato has examined the association between fingertip whorls and the development of breast cancer. The investigators collected fingerprints from 119 women, including 34 who had breast cancer, 53 who were considered at high risk of developing breast cancer, and 32 who were free of the disease and not considered at high risk. This pilot study showed that over 32 percent of the breast cancer patients had a total of six or more whorls on their fingers compared with 3.1 percent of the controls. The high risk women fell in between. In this sample, 95 percent of the women with six or more whorls on their fingers had breast cancer or were at high risk of developing it.

Dr. Plato cautions that these findings cannot be used at this point to predict whether or not an individual might develop breast cancer. "Even though these results were dramatic, a relatively small sample of women was used. Further research is necessary before this information can have practical diagnostic applications for individuals," he explains. "As more data become available, it is hoped that this research leads to the development of methods which, along with other diagnostic tools, will help identify potential breast cancer patients," says Dr. Plato.

To investigate the dermatoglyphic traits which might indicate an inherited tendency to develop a disease or condition, prints must be collected on parents, children and other relatives of affected individuals. Dr. Plato and his colleagues are collecting finger and palm prints from breast cancer patients and as many of their family members as possible for clues to the development of this disease.

The best example of an association between dermatoglyphics and disease is in Down's syndrome patients who usually have characteristic patterns called ulnar loops on all fingers and have a high frequency of single palmar creases called Simian lines and Sydney creases. Although these creases are also found in people without this condition, they are far less common. Sydney creases are also found in large numbers among leukemia patients and their siblings, but not among their parents. About 25 percent of the leukemia patients studied have Sydney creases compared to three or four percent among people who never develop leukemia.

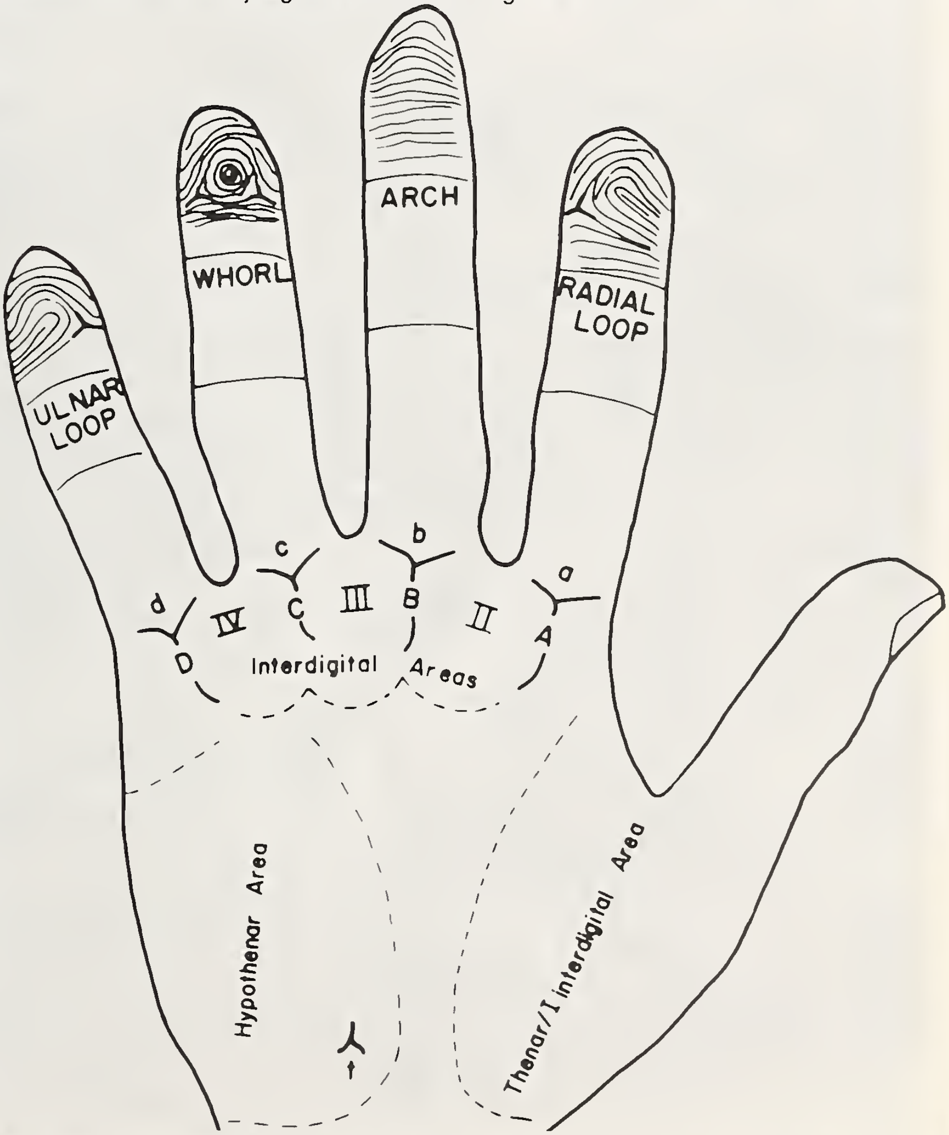
Dr. Plato first began collecting palm and finger prints in 1962 while doing research on neurologic disorders in Micronesia for the National Institute of Neurological and Communicative Disorders and Stroke. "Traveling from island to island on a coconut boat, I sometimes had to wait for the health officer to complete his examinations. To use the time I decided to collect finger and palm prints from the natives to see what interesting and useful patterns I might find."

"At first many people considered it a joke that I was studying finger and palm prints," remarks Dr. Plato. "They would ask if I was trying to tell their fortunes. Now, clinicians are appreciating the importance of dermatoglyphics and regarding it as the serious undertaking that it is. It is becoming routine in some types of journal articles, especially in pediatrics, to describe the dermatoglyphic characterizations of certain conditions. The study of dermatoglyphic traits may one day become an intergral part of clinical medicine." In 1974, Dr. Plato and scientists representing the fields of anthropology, biology, medicine and related disciplines, established the American Dermatoglyphics Association and Dr. Plato became its first president.

As clinicians and other scientists have learned about Dr. Plato's work, many have contributed palm prints and finger prints from their patients or from groups with which they are working. Some are sent from various parts of the world, including Tibet, the Solomon Islands, the Peruvian Andes and Amazonian jungles. Dr. Plato and his colleagues recently received prints taken from babies who were victims of sudden infant death syndrome. The investigators will analyze these in the future.

Dr. Plato hopes that scientists will continue to send these prints for current studies and future analysis, but he encourages his colleagues to contact him first to learn the proper procedures for recording them. Prints that are improperly taken or labelled may prove useless. Through the efforts of Dr. Plato and his collaborators, the collection has grown to be the largest of its kind in the world.

"The study of dermatoglyphics has many potential benefits," says Dr. Plato. "It can be used as an aid for genetic counseling and to help us understand the development of the fetus during the first trimester of pregnancy. Hopefully, it will also enable us to identify carriers of genetic diseases before they show symptoms or pass these genetic tendencies to future generations, and help us diagnose some of the diseases of middle and old age." ■



Fingerprints are analyzed by noting the numbers, locations and other characteristics of fingertip patterns, called whorls, loops and arches.

NIH PHOTO 1873

Studies Indicate that Retirement is Not Detrimental to Health

Esther Solomon

The popular notion that retirement has an adverse affect on physical and mental health is being challenged. Evidence is building which suggests that, while individuals differ, on the average retirement has only a minimal effect on health.

In a series of studies supported by NIA and the Veterans Administration (VA), Dr. David J. Ekerdt and Dr. Raymond Bosse at the VA Outpatient Clinic in Boston found that workers who retired experienced no greater declines in health than those who continued to work. The investigators used three methods to evaluate the health of workers and retirees: self-ratings of general health, a checklist of specific physical complaints, and medical examinations.

Many people keep healthy and active during the retirement years. Evidence from recent NIA studies on retirement shows that workers who retired experience no greater declines in health than their peers who continued to work.

NIH PHOTO 1874

The studies used volunteers from the Boston VA's Normative Aging Study (NAS) which was begun in 1963 to study aging in 2,000 healthy community-living men born between 1884-1945. All NAS participants over 52 receive medical exams every three years. Some of the results of these medical examinations were used for the studies of health and retirement.

Retirement from work does not necessarily lead to health deterioration as many people believe. Mack Schwab, a 73-year-old athlete from Columbia, Marylands runs 30 miles a week to keep in shape.

NIH PHOTO 1875

In one study, the investigators wanted to find out how retirees viewed their own health status before and after retiremen as compared to men of the same ages who continued to work. In 1975, they asked 559 older men, all nonretired participants of the NAS, to complete questionnaires in which they rated their physical health as good or poor and indicated whether or not they had any serious health problems.

In 1978, after 112 of these men had retired, the recent retirees and their age peers who continued to work were again asked to rate their physical health. Over the three-year period both groups perceived some decline in physical health. This decline was similar for both the retirees and workers. Thus, Drs. Ekerdt and Bosse find no statistical association between retirement and this decline in self-reported health.

When the retirees were asked if retirement had a "good" or "bad" effect on their health, 38 percent reported a "good" effect. The investigators attribute this improvement partly to more relaxed lifestyles, particularly since the perception of improved health was more frequent among those retirees whose jobs had been more stressful. Only two percent reported that retirement had a "bad" effect on their health.

The retirees themselves had expressed anticipatory fears that retiring wou harm their health. When still working, 68 percent projected health worries for their retirement. When questioned after retirement, only 38 percent reported worrying about their health.

In a related study, the researchers used specific physical health complaints as an index of health status. Using a scale of 97 questions about health problems, they compared 171 NAS participants who retired between 1972 and 1978 with 386 workers in the same age ranges.

As expected, some individuals in both groups reported more health complaints over time; however, Drs. Ekerdt and Bosse found that those who retired reported about the same number of health complaints as those who continued to work. Circumstances often thought to be stressful for retirees, such as compulsory retirement and living on a reduced income were not statistically associated with any increase in health complaints among these volunteers. Also, the number of health complaints among retirees was not affected by age at retirement, the length of time retired, whether or not they worked part-time during retirement, former occupational level or marital status.

Similar conclusions emerged from still another study that used independent ratings of physical health status based on medical examinations. Over 600 men had two medical exams given three years apart. At the time of the first examination, all were working. By the time of the second examination, 229 men had retired. A comparison of retirees' health ratings with the health ratings of men who continued to work showed a similar experience of health change, and no health declines attributable to retirement. There was also no relationship between actual health declines and compulsory retirement or retirement from prestigious occupations.

All of these studies were conducted by excluding men who retired for health reasons in the first place. Men who retired primarily because of illness or disability (about 20 percent of the sample) differed markedly from those who retired for other reasons. More often, they retired early and unexpectedly and were five times more likely to rate their health as poor or to claim to have serious health problems. It may be because of these disability retirees that retirement is often viewed as the cause of health declines.

Although it is sometimes reported that there are periods after retirement which may be stressful and cause health problems, these investigators found no particular time within four years of retirement when health risks were especially great.

These studies also showed that the transition from work to retirement tends to be characterized by continuity rather than disruption. Moreover, retirees did not see themselves as more involved in such leisure activities such as exercising, reading, or socializing than their working peers of the same age.

"Retirement is an important feature in people's lives," says Dr. Ekerdt. "Our intention in these studies is to provide accurate and helpful information about the experience of retirement to those facing retirement, to physicians who may recommend retirement to their patients, and to people involved in planning services and programs for older adults."

"I think that some people will be surprised by these conclusions," Dr. Ekerdt continues. "It is a widely held view that retirement often has a negative effect on health. Everyone seems to know someone who retired and then became ill or died. Often the illness or death becomes associated in the person's mind with retirement.

"People planning to retire should be concerned about a lot of things—such as financial planning or leisure activities—but our evidence shows that the effect of retirement on health should not be a major concern," Dr. Ekerdt concludes. ■

Retirees can enjoy many years of fulfilling activities. Studies supported by NIA are challenging the widely-held view that retirement often has an adverse effect on health.

NIH PHOTO 1876

Chronic Disease in the Aged Studied at Teaching Nursing Homes

Donna Maxwell

As a result of advances in medical care, many acute diseases which once limited life expectancy have been overcome. Today, many people live to celebrate their 70th, 80th, or 90th birthdays, a time when chronic disease is most prevalent. Particularly when there is no family to offer care and support, chronic disease can result in the need for long-term care in the community, or, in some cases, in one of the nation's 19,000 nursing homes. Typically, these homes are isolated both geographically and academically from teaching medical centers. For this and other reasons, the research community has shown limited interest in chronic disease among the aged.

In response to this need, NIA recently awarded teaching nursing home grants to the Albert Einstein College of Medicine in New York, and a consortium of the Philadelphia Geriatric Center (PGC), the Medical College of Pennsylvania, and the University of Pennsylvania. While both the NIA and several private sector organizations simultaneously developed the concept of the teaching nursing home, the scope of the NIA program is limited to supporting research on geriatric health problems. The main goal of the NIA teaching nursing home programs will be to develop increased knowledge of chronic diseases and their effect on older adults.

The five-year teaching nursing home grant awarded to the Albert Einstein College of Medicine totals $2.96 million. The long-term care facilities involved are Beth Abraham Hospital, Morningside House Nursing Home, and the Hebrew Home for the Aged. The participating institutions are Bronx Municipal Hospital Center, the Montefiore Medical Center, and the College of Mt. St. Vincent.

The setting for this teaching nursing home is the Bronx. It is the third largest borough in New York City with approximately 17.3 percent of the population 60 years or older. While overall population of the Bronx has decreased, the number of older persons has continued to grow. By 1984/85 it is estimated that almost 50 percent of the population in the Bronx will be 75 years or older.

The project's principal investigator, Robert Katzman, M.D., is Professor and Chairman of Neurology at the Albert Einstein College of Medicine. He has done extensive work in the areas of the neurology of aging and senile dementia.

The project will address some of the more prevalent problems found in nursing homes today, including senile dementia, osteoarthritis, and falls among the elderly. Often these problems are not treated in hospitals.

Senile dementia is a term used to describe a large number of conditions affecting intellectual functioning. These conditions are among the most common reasons for institutionalization among the elderly and affect nearly half of all residents in skilled nursing care facilities. Little is known about the cause, history, or management of dementia in later stages. The needs of many elderly patients suffering from dementia have largely been ignored.

As part of their research into dementia, investigators at Einstein are evaluating the effectiveness of physostigmine, a drug which may be capable of improving memory in patients with some forms of senile dementia. In addition, researchers will conduct a longitudinal study of a significant number of demented patients, in order to track the progress and course of the disease. Researchers will try to further isolate criteria for diagnosing Alzheimer's disease (the most common form of senile dementia) and multi-infarct dementia. The correlation between cognitive changes in Alzheimer's disease and genetic factors will also be examined. Studies such as these have the potential for identifying the causes of Alzheimer's disease and other forms of dementia.

The second area of study at Einstein focuses on osteoarthritis in the elderly. Osteoarthritis is probably the most common source of debilitating pain among the elderly. It is a degenerative joint disease which most often affects the knees, hips, or spine. Doctors at Einstein will take a closer look at osteoarthritic joints and study the biochemical interactions of membrane, fluid, and cartilage in patients who require surgical treatment for the condition. The researchers will study the process by which osteoarthritis develops and worsens, and will test certain drugs which are thought to inhibit that process.

Although research in geriatric medicine is the major goal of NIA's teaching nursing home grants, the program also allows students to receive specialized training in the needs of the elderly. Here, a physician examines a nursing home patient while a medical student observes. (Photo courtesy of Albert Einstein College of Medicine).

NIH PHOTO 1877

A major subproject of the grant to the Albert Einstein College of Medicine (AECOM) involve the study of brain function and senile dementia. This elderly man is receiving neuropsychological testing from an AECOM staff member. (Photo courtesy of Albert Einstein College of Medicine).

NIH PHOTO 1878

In addition, researchers at Einstein will conduct a two-phased study concerning how balance and gait relate to falls in the elderly. Unexplained falls, a frequent problem among nursing home residents, contribute to untold accidents, fractures, and anxiety among the elderly. During the first phase of the research, a retrospective study will be done involving a select group of chronic fallers in the home and a group of control subjects. Both groups will undergo specialized testing and clinical assessment to identify any differences that may be present. In the second phase of the study, the investigators will look for early signs of neurological dysfunction in nursing home patients in an attempt to determine why the elderly fall as frequently as they do. Eventually, they hope to develop suggestions for ways to prevent such falls through the intervention of the health care team.

The five-year teaching nursing home grant awarded to the Philadelphia consortium totals $4.47 million. The Philadelphia Geriatric Center (PGC) houses over 1,000 residents. In addition to 550 residential beds and 486 long-term care beds, there is a small, 78-bed acute care hospital which primarily serves residents of PGC. There is also a home care program which serves over 1,000 patients each year and a rehabilitation day care center which handles 15-17 patients each day. A comprehensive consultation and diagnostic service is also available. The investigators plan to use all of these resources as well as others to recruit research subjects. Other participating institutions are Faulkeways and Pennswood, two life-care communities, All Saints Hospital, and Elmyra-Jeffries Nursing Home.

The principal investigator, Donald Kaye, M.D., is Professor and Chairman of the Department of Medicine at the Medical College of Pennsylvania. He is also Director of Research at the Philadelphia Geriatric Center. His particular area of interest is the study of infectious diseases.

This program will involve a number of studies including research to determine factors which would affect an older person's risk of acquiring a urinary tract infection and what significance the infection would have in terms of morbidity and mortality. After identifying subjects who develop such infections, the investigators will treat all infections in a group of patients with an antibacterial drug, trimethoprim. Patients will be closely monitored to determine the effects of treating all episodes of infections.

Also, the researchers will compare two types of rehabilitation for stroke patients. While the number of stroke-related deaths has dropped in recent years, the effects of stroke make it one of the more debilitating afflictions of aging. Patients accepted into this study will be divided into two therapy groups. One group will receive intensive rehabilitation with cognitive therapy as well as routine rehabilitation, while the other group will receive routine rehabilitation only. The investigators believe that challenging stroke victims with learning tasks will cause increased functional activity and increased blood flow to certain regions of the brain. By selecting tasks which would involve the affected areas of the brain, researchers can determine if routine rehabilitation may be improved by the addition of supplemental learning tasks directed at specific areas of the brain by monitoring blood flow in that region of the brain.

An elderly subject answers a questionnaire with Dorothy Pfohl, RN, BS, Patient Registry Administrator of the teaching nursing home project at the Philadelphia Geriatric Center. (Photo courtesy of the Philadelphia Geriatric Center). NIH PHOTO 1879

Researchers will also examine the use of the PET (positron emission tomography) scan in the study of dementias. The investigators hope to identify changes in blood flow and brain metabolism associated with several types of dementias and to explore the potential of PET as a tool for the early detection and diagnosis of dementias. In this aspect of the study, investigators will examine patients with Alzheimer's disease, multi-infarct dementia, and Parkinson's disease.

Also, as part of the grant, the researchers will study sleep apnea which involves frequent and potentially life-threatening interruptions of breathing during sleep. There is a suggestion that this disease is common among the elderly. The first objective of the researchers is to determine whether aging indeed predisposes people to sleep apnea. In addition, the investigators will examine the consequences of the disease in elderly subjects and particularly determine whether daytime hypersomnolence in the elderly is a consequence of sleep apnea syndrome. The researchers will also investigate the mechanisms responsible for the development of sleep apnea in elderly subjects. They will compare breathing patterns during sleep in young and elderly subjects as well as the effect of sleep on the ventilatory responses to hypoxia (oxygen deficiency) and hypercapnia (excess of carbon dioxide in the blood) in both groups. The effect of sleep on upper airway function will also be contrasted in old and young subjects.

A further study focuses on exercise in the elderly. Research will first establish normal cardiac pulmonary function, and exercise parameters in the elderly. Investigators will also assess overall health and activities of daily living of their subjects. Subjects will then be divided into two groups: two exercise groups and one control group. The study will last for five years and attempt to measure effects of exercise on physiology, maintenance of independent living, morbidity, and mortality.

In recent years, many organizations have begun to recognize the need to promote geriatric medicine and clinical research on aging. From its inception, NIA has spurred medical educators to incorporate geriatrics into their curricula and clinical training programs. If successful, teaching nursing homes like those beginning at the Philadelphia Geriatric Center and the Albert Einstein College of Medicine could bring geriatric medicine even further into the mainstream of medicine. In addition, the Robert Wood Johnson Foundation, the W.K. Kellogg Foundation, and the Beverly Foundation have begun to support the concept of teaching nursing homes.

Teaching nursing homes are not intended to set standards for nursing homes across the country, nor are they intended to divert funding or personnel away from services that offer alternatives to nursing home care for the elderly. Rather, they are intended as community-based sites to promote research and training and to encourage and upgrade services for both the institutionalized and non-institutionalized elderly. ■

Reaction Time Does Not Have to Slow with Aging

Donna Maxwell

The idea that reaction time slows with age is probably one of the more firmly entrenched beliefs about aging. However, research by NIA grantee Alan Baron is revealing that in many instances even this deficit may be overcome through training.

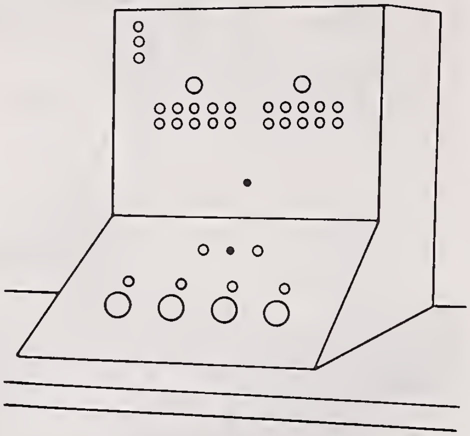
A three-year research project being conducted at the University of Wisconsin-Milwaukee focuses on performance deficits in older people. The research is showing that when older people are asked to do routine tasks, time pressure has little or no effect on their performance. When asked to perform new tasks however, time pressure has a negative effect on performance—an effect which can be overcome, however.

In the past, researchers have studied physical performance deficits in the elderly, but comparatively little work has been done to study the psychological processes involved in performance. Research which has been done on age-related behavioral deficits has typically shown that when given unlimited amounts of time, older people can learn new tasks effectively. However, in real-life situations, people are rarely given unlimited time to complete a task. Studies of the elderly have shown that the time needed to actually do the task is not the main problem. Rather, the problem lies more in the time it takes them to decide what to do. An elderly tennis player, for example, probably does not need extra time to swing the racket, but he/she does need extra time to decide how and when to swing it.

To study reaction time in the elderly, Baron included both old and young men in his study. The younger subjects (18-25 years) were college students recruited through advertisements and the University employment office. The older subjects (62-80 years) were drawn from the University's "Over 62" program for older adults. Subjects were matched according to health, intelligence, education, and socioeconomic background.

The investigator simulated a real-life job situation in the laboratory by asking subjects to come in as if they were reporting for a part-time job scheduled for one-hour shifts. Baron found that by using operant conditioning (immediate feedback and correction), payment being one example, he was able to reinforce rapid learning and high performance. The subjects earned money either by performing well during the sessions, or by completing all scheduled sessions, at which time they were awarded a bonus.

A tabletop apparatus, reminiscent of an upgraded computer game, was selected for the research. Subjects were instructed to press the keys on the lower portion of the console imitating sequences determined by the light patterns at the top. If correct, the subject was signaled by a light on the keyboard. If incorrect, a different light came on and the respondent was penalized by having to wait a few seconds for the sequence either to begin again or to continue from the point of error.



This diagram illustrates the table top apparatus used in Dr. Baron's research. Young and old subjects pressed keys on the lower portion of the console imitating sequences of light patterns at the top.

NIH PHOTO 1880

Each time the men reported to the laboratory, they began with a test of their ability to learn new information. Working on the console, they responded to a pattern of lights which varied from session to session. A total of 44 combinations of 10 lights each was used in this acquisition component of the program.

Alternating with the acquisition component every five minutes, the performance component of the program involved a fixed combination of 10 lights which appeared repeatedly. Progressively less time was given to complete each sequence.

The older men responded efficiently in the performance component except at the very shortest interval. This suggests that even a well-established response pattern can be resistant to the negative effects of time limitations. In the acquisition component, greater time pressure resulted in increased errors by older subjects, but had little effect on younger men.

Baron's work is unusual in several aspects. Earlier studies involving psychological and behavioral performance deficits in older people often used impaired, sometimes institutionalized individuals as subjects. When presented with a complex testing situation, these individuals often became tense and anxious about their performance. Baron's subjects were healthy, active individuals from the community. His goal was not to challenge them, but to improve their skills through a graded series of tasks.

Other related studies of learning and memory have not allowed older adults to draw on their years of accumulated experience and wisdom. Often, the procedure has ended before the older person has had a chance to adjust to the testing situation. Baron's work enables the behavior of older people to be observed over relatively long periods of time. Respondents sign a contract agreeing to participate in the research for an average of 40 hours spread over a period of two to four weeks. This prevents the results from being affected by the person's reaction to the procedure itself. As an added measure, Baron and his colleagues periodically administer a standardized psychological test to measure anxiety levels of the subjects.

Baron and his colleagues also found that age differences could be substantially reduced by restarting the pattern following an error rather than allowing the respondent to immediately correct the error and then continue. By restarting from the beginning, a steady pattern for learning the sequence was established.

Baron's work, which is being expanded, will include an assessment of whether changes in the performance of older subjects can be considered permanent and whether the methods which succeeded in the laboratory can be transferred smoothly to everyday life. His goal is to develop specific techniques which the elderly can use to improve performance deficits, similar to the remedial programs used to help college students improve their study habits.

Baron subscribes to the disuse theory first proposed in the 1920s to explain why certain skills fade with age. The theory suggests that when skills are unused they gradually become weaker and eventually are lost. Society believes that once a person passes middle age, retirement, relaxation, and inactivity must soon follow. Consequently, certain skills go unused in the elderly and are weakened. Baron believes that an individual who is willing to devote enough time and energy can resharpen skills which have weakened through disuse.

Baron and his colleagues feel that their findings will be useful to answer questions about employment, social security, and retirement as the population ages in the years to come. He feels that eventually retirement will have to be determined on some basis other than age.

While it is a big step to take, the results from a sheltered laboratory environment and attempt to apply them to the real world with numerous distracting stimuli, Baron and his colleagues feel that their work may be applicable to real-life situations. Baron's research has made it clear that older people are capable of being trained and motivated to learn new information even if time constraints are imposed. ■

Nursing Home Staff Attitudes Can Affect Client Behavior

Research in the behavioral sciences is showing that, even in nursing homes, dependent and unhappy patients can often recover a degree of independence when their daily activities promote interaction with others, self-care and a sense of control. Routines which stimulate independence can result not only in increased alertness and involvement, but also in improvements in general health.

In an effort to increase knowledge about nursing home caregivers' attitudes, and about how attitudes are related to caregiving, NIA grantees Eva Kahana of Wayne State University and Asuman Kiyak of the University of Washington, sampled 423 employees of nursing homes and community service agencies in Detroit and Seattle. They found that in general, most service staff portray positive attitudes toward the elderly, hold relatively few stereotypes, and tend to encourage independence rather than dependence in elderly clients.

Since not all staff attitudes are positive, however, the researchers also focused on how attitudes among people who provide services to the elderly are related to their behavior toward older clients and to job satisfaction. The results of their study suggest that employees' attitudes toward the elderly and toward their own aging largely determine whether they will encourage independence among their clients: the more positive the attitudes, the greater the chance that the staff will foster independence.

In the attempt to understand staff attitudes, employees were questioned about their feelings toward elderly clients, the elderly in general, and their own aging and death. The investigators also recorded each employee's age, sex, educational level, previous training or experience with the elderly, and history of interactions with older relatives. They also looked at such environmental variables as the size, staffing patterns, atmosphere, and ownership of the institution or organization.

The researchers found that employees who were married, over 50 years of age, had training in gerontology or had worked previously with the elderly, were more satisfied with their jobs in general and, in turn, were more apt to like their clients and to promote independence among them. These workers also had more positive attitudes about their own aging and death and held fewer negative stereotypes about the elderly.

A nursing home employee helps an elderly woman out of her wheelchair. NIH PHOTO 1881

Both volunteers and administrators were more likely to promote independence. Generally, nurses' aids reinforced dependence on caregivers and the family. Part-time workers, more so than full-time workers, were likely to foster independence. Employees on night shifts also tended to encourage independence among clients.

In community agencies, the investigators found that employees encouraged independence and were generally more positive toward elderly clients and their own aging than were nursing home employees. This may be explained by the fact that community service agencies usually serve more healthy, vibrant elderly clients than do long-term care facilities.

The study also explained staff behavior in terms of intention to leave, and actual job turnover. Thirty-five percent of the staff in community agencies as well as institutional facilities expressed an intention to leave their jobs and 39 percent of staff actually left within the one-year follow-up period. Satisfaction with work, with supervisors, and with pay best discriminated between those preferring to leave and those intending to stay.

The researchers conclude that nursing homes or community service organizations might want to consider hiring employees who hold positive attitudes toward the aged even if their education is limited or if they prefer to work only part-time. Employers might also give extra consideration to more mature workers since the research has revealed them to be better suited to caring for the elderly. These findings suggest potential criteria for future staff selection and training in community organizations and long-term care facilities serving the elderly. ■

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National Institutes of Health
Building 31, Rm. 2B-10
Bethesda, Maryland 20205

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES   Public Health Service   National Institutes of Health

News&Features
from NIH

June 1983

Researchers at a new pain clinic at NIH are studying acute and chronic pain to learn more about how to treat pain and to develop better methods of pain assessment. The multidisciplinary facility will enable all the NIH Institutes to pool their knowledge and exchange ideas. The clinic is currently accepting qualified patients for its studies. See page 2

Children with a relatively rare disorder, Asperger's syndrome, are often misdiagnosed as autistic or schizophrenic. At a recent seminar sponsored by the National Institute of Mental Health, (NIMH) the syndrome was described as a handicap that parents could learn to manage. In the future, correct diagnosis will keep physicians from treating these children with drugs that are not effective. See page 7

The National Diabetes Advisory Board has developed a guide for the treatment of five of the major complications of diabetes.

The guide incorporates a consensus of experts as to the most advanced modes of treatment for: complications of pregnancy; kidney failure; ophthalmological complications; acute ketoacidosis; and foot problems, which can often result in the need for amputation.

It is hoped that management of problems in diabetes in accordance with the guide could result in improved care and reduced hospitalizations for diabetic patients. See page 10

A new treatment for premature infants with respiratory distress syndrome (RDS) is being tested by researchers at the University of California, supported by the National Institute of Child Health and Human Development (NICHD).

The procedure involves the application of a lung lubricant which inflates the baby's lungs after birth. The lubricant, called "surfactant," is normally produced by the fetus prior to delivery. In very premature infants, however, insufficient amounts of surfactant are produced, and this is often fatal.

Now researchers have found that purified surfactant, isolated from amniotic fluid from full-term cesarean deliveries and given to premature babies with RDS, significantly improved their ability to breathe. See page 13

COVER:

Dr. Bruce Baum, chief of the Clinical Investigations and Patient Care Branch, NIDR, is collecting saliva samples to measure the flow rate of saliva.

The saliva samples are collected on ice for biochemical analysis.

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Editorial Staff

Mary Donovan
Editor

Susan Gerhold
Associate Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

NIH News Branch
Building 31, Room 2B-10
Bethesda, Maryland 20205

Phone:
(301) 496-2535

Dental Institute Unveils Pain Clinic in Ambulatory Care Research Facility

Jody Dove

Last March the National Institute of Dental Research (NIDR) opened the first multidisciplinary pain clinic in the United States devoted exclusively to research. The clinic is located in the Clinical Center's Ambulatory Care Research Facility (ACRF).

In collaboration with other NIH Institutes, NIDR researchers are conducting studies of acute and chronic pain to generate knowledge about pain mechanisms and the treatment of pain and to develop better methods of pain assessment. Consultation in difficult pain management problems is also offered by the research facility's team of scientists and clinicians.

The opening of the clinic has evolved from the NIDR's longstanding interest in pain research. Pain is a central concern of dentistry because it is a common symptom of most oral and dental problems; about 25 percent of all chronic pain problems are associated with the face and oral cavity.

Under the direction of Dr. Ronald Dubner, chief of the Neurobiology and Anesthesiology Branch, NIDR, scientists have been assessing experimental and clinical pain and the use of new agents for pain control since 1974. These investigators have also been studying how the brain codes messages related to painful stimulation, and how these signals can be modified at different levels of the nervous system by chemicals such as morphine-like substances produced by nerve cells.

"Our knowledge about pain has increased rapidly in the past fifteen years and we now have a unique opportunity to apply this knowledge to the clinical situation," said Dr. Dubner.

The idea of starting a multidisciplinary clinic began in 1979 when the NIDR submitted plans to Dr. Mortimer Lipsett, then director of the Clinical Center, to initiate a cooperative pain research facility. Approval was granted and the clinic was allocated space in the planned ACRF. The new clinic will enable researchers and clinicians in all of the NIH Institutes to pool their knowledge and exchange ideas about the pathophysiology and treatment of pain.

Institutes presently participating in the program include the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Mental Health and the Anesthesiology Department of the Clinical Center. The Uniformed Services University of the Health Sciences is also involved in some of the studies.

NIDR staff comprise the nucleus of the clinic: Dr. Mitchell Max, a neurologist, serves as clinical coordinator; Dr. Richard Gracely, an experimental psychologist, is responsible for pain assessment; Dr. Raymond Dionne, a clinical pharmacologist and dentist, provides expertise on pain control agents; and Peggy Wirdzek is the nurse coordinator.

Major advances in neuroscience have led to greater knowledge about the basic mechanisms involved in pain transmission and modulation. Further information is needed, however, before dentists and physicians are able to treat many painful conditions for which relief is not yet available.

"There have been tremendous advances in terms of our understanding of how the pain system works on a cell by cell basis," explained Dr. Max. "Yet we still need to find out how the pieces fit together, so we can translate this knowledge into clinical breakthroughs. Much of this information can be provided only by our patients."

Pain research remains a complicated field because pain assessment is a subjective phenomenon. Pain serves as a signal of impending or already present tissue damage. But the area of the body in which the pain occurs and a patient's cultural background, emotional state, previous sensory experience, and the significance of a given situation can influence reaction to pain.

To help standardize pain assessment, the NIDR scientists have developed new scales for verbally assessing pain that more adequately quantify the multidimensional aspects of the pain experience. Patients are asked to separately report two major aspects of pain: its unpleasantness and its intensity.

The research program comprises two components—an acute pain program and a chronic pain program.

The acute pain studies center around a dental model for assessing surgical and postsurgical pain associated with the extraction of third molars (wisdom teeth). The model is excellent because findings from these studies have general applicability in the study of postsurgical pain at other sites.

Investigators are evaluating the effects of combinations of analgesic drugs and sedative agents on pain, anxiety, and patient cooperation. They have found that using a long-lasting local anesthetic in combination with a nonsteroidal anti-inflammatory drug significantly reduces postoperative pain. And about half the patients reported no postoperative pain at all.

Other studies include the correlation of plasma levels of various neurochemicals with pain reported by patients during and following the surgical procedure; the assessment of pain using the newly-developed pain scales; and the mechanisms of the placebo effect. The effect of stress in activating the brain's own pain-suppressing mechanisms is also under investigation.

The chronic pain program includes studies of myofascial pain, diabetic neuropathy, Parkinson's disease and cancer.

Pharmacological and non-pharmacological approaches to the treatment of myofascial pain are being explored in patients suffering from pain and dysfunction of the temporomandibular, or jaw-hinge, joint. The muscles often go into a spasm or cramp, leading to tissue damage, pain, and tenderness. Treatment for

Dr. Ronald Dubner, chief of the Neurobiology and Anesthesiology Branch, NIDR, talks with Dr. Mitchell Max (right), a neurologist, who serves in the Pain Clinic as clinical coordinator.
NIH PHOTO 1883

Peggy Wirdzek, nurse coordinator, (standing), and Dr. Raymond Dionne, clinical pharmacologist and dentist, work with the NIDR staff in seeing patients with various types of pain.
NIH PHOTO 1884

Ruth Schilling delivers a thermal experimental pain stimulus to a patient who rates his perceived pain by a verbal response. The patient also receives intravenous drugs with pre- and post-experimental testing.
NIH PHOTO 1885

this condition has been varied and has sometimes consisted of therapies such as grinding away high spots on the teeth or surgery of the joint. The researchers will compare outcomes in groups of patients treated with drug therapy and other more conservative forms of treatment.

Some diabetic patients develop nerve damage, particularly to nerves in the feet. Scientists in the research clinic are examining patients who have nerve pathology accompanied by pain, and are evaluating the effectiveness of amitriptyline, an antidepressant drug, in controlling the pain. Previously conducted animal studies have demonstrated that amitriptyline increases the availability of serotonin, a chemical released at some nerve endings that inhibits painful sensations. Researchers are trying to learn whether the drug is effective in diabetic patients because actual pain relief occurs or because the patients become less depressed and hence report less pain.

Patients who have Parkinson's disease undergo a degeneration of a portion of the brain stem called the locus coeruleus. The locus coeruleus is believed to modify the action of the brain's own pain-suppressing system that involves endorphins (morphine-like natural substances). Scientists in the clinic are trying to find out how this atrophy affects pain perception, and if these patients experience pain more intensely. They are also determining whether morphine acts on patients with Parkinson's disease in the same manner as it affects other people.

The NIDR and NCI scientists will be examining alternatives to low-dose narcotics in cancer patients with pain. Flurbiprofen, an investigational new drug that is a member of the aspirin family, will be employed in this study. The drug has the analgesic strength of narcotics, but does not produce grogginess and nausea.

In another study, investigators will evaluate the effectiveness of a novel opiate drug, DADL-enkephalin, in patients who no longer receive relief from morphine. The brain contains three or four opiate receptors that are involved in the suppression of pain signals. Morphine works specifically on one of the receptors, but as a patient becomes tolerant to morphine, that receptor no longer functions. DADL-enkephalin may be a useful alternative drug in these cases since it acts on a different receptor.

The research clinic will also seek to develop and test specially designed games to measure pain in young children with cancer. This study will lay the groundwork for research on pain treatment in children. The effectiveness of hypnosis in children undergoing diagnostic procedures such as bone marrow aspiration, and the usefulness of morphine infusions in children with severe pain will be examined.

The clinic is evaluating the effects of deep brain electrical stimulation in the treatment of intractable chronic pain. This controversial technique, which requires brain surgery, is being used in patients at the Medical College of Virginia who have low back pain unsuccessfully treated by other methods. The stimulator presumably activates the brain's pain-suppressing mechanisms and thereby reduces the patient's pain. The patients are admitted to the pain research clinic for independent testing of the effectiveness of this procedure.

The pain research clinic is currently accepting qualified patients for its research studies. Patients who have pain problems coinciding with the research interests of the new clinic should have their dentists or physicians call or address letters of referral to Dr. Mitchell Max, c/o the Clinical Pain Section, NIDR, NIH, Building 10, Room 1B-15, 9000 Rockville Pike, Bethesda, MD. 20205 (301-496-5483).

"Patient participation is essential for the success of this program. Those who become involved in these studies are making valuable contributions which hopefully will lead to new and improved methods of pain control in the future," stated Dr. Dubner. ■

MS Research: Looking for Constants in a Fickle Disease

Diane Striar

"Hundreds of treatments, from the poisonous belladonna plant to strychnine, have been tried on multiple sclerosis in the last century," says Dr. Dale McFarlin, chief of the Neuroimmunology Branch of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). "But clinical research on the disease has long been hampered by the nature of MS—a disorder with spontaneous periods of remission or improvement which can mask the true effects of an apparently successful treatment."

The belladonna era is over. But modern scientists must still contend with the fickleness of this disorder. They must also deal with a number of other factors which make multiple sclerosis research difficult to conduct. According to Dr. Henry McFarland, assistant chief of the Neuroimmunology Branch: "We have had patients on experimental protocols who got better while they were being treated. The problem is we couldn't tell whether it was the treatment itself that helped, or whether they could have gotten better by themselves without treatment."

Multiple sclerosis (MS) is a disorder that destroys the protective myelin sheath surrounding nerve fibers, producing such symptoms as weakness, pain, and blurred or double vision. Most MS patients experience these symptoms sporadically, in episodes called exacerbations followed by periods of remission. For some of these patients, time will not worsen the severity of the symptoms; in others, it will. There is also a different, chronic form of MS in which symptoms are always present and continue to become progressively worse. This variation in the display of symptoms makes it difficult to predict how a patient would react in a research study.

Furthermore, there is no laboratory test that can confirm an MS diagnosis, a necessary step in selecting research patients. "Although some lab tests such as studies of spinal fluid can help in MS diagnosis, MS is still primarily diagnosed according to a doctor's clinical examination," says Dr. McFarland.

Even a neurological exam, however, may not produce the clear-cut diagnosis required. A patient's symptoms may indicate "possible," "probable," or "clinically definite" MS. Using a "possible" MS patient in research is risky, for if the disease is not really MS, data gathered on that patient would be of little value to the study. More important, "possible" MS patients might actually have another, treatable disease that might be neglected until an accurate diagnosis is made.

"Probable" MS patients can be useful subjects for some research studies, for there is only a small chance that these people have been incorrectly diagnosed. But it is the "clinically definite" MS patient who yields the most reliable research data. Identifying this patient from among those in other diagnostic categories is part of the MS investigator's burden.

Although scientists have not yet identified the cause of MS, they speculate that an infectious agent or an overactive immune response which attacks the body's normal tissues may be responsible for the neurological disorder. Since the major portion of the immune response is under genetic control, Drs. McFarlin and McFarland are studying identical and fraternal twins for clues to the disease. One or both twins in each set have multiple sclerosis. The scientists hope to discover a particular genetic factor that may relate to the cause of MS.

Throughout the study the investigators have been hampered by the lack of a diagnostic laboratory test for MS. "The research was set up to study people who had either "probable" or "clinically definite" MS, and their normal twins. However, when we started to examine the unaffected twins," says Dr. McFarland, "we found that some of them had minor abnormalities and also minor changes in their spinal fluid. The question is: do these 'normal' twins have MS or don't they? It's critical for this study to be able to say which twins are affected and which are not. So, this has been a problem."

Despite this difficulty, the NINCDS Neuroimmunology Branch has made progress. One research finding may even help scientists develop a laboratory test for MS. When NINCDS investigators analyzed the white blood cells of the twins, they found that in four sets the twins with MS had a greater immune response to measles than did the unaffected twin.

"When presented with measles virus, the white blood cells of the MS twin divided more often than those of the normal twin. Also, the MS twin's white cells killed more of the measles virus-infected target cells," says Dr. McFarland. He hopes to clarify the significance of this work by studying the immune systems of other MS twin sets.

The study of twins has also yielded early data which may relate to the cause of MS. "Information collected so far indicates that the normal twin in an MS identical twin pair has a higher-than-average chance of eventually developing the disease. But the odds diminish as the normal twin ages: the longer the twin remains MS-free, the less likely he or she is to develop the disease," says Dr. McFarland.

There are a number of older twin sets in which only one twin has MS. "This suggests that environmental factors are at least as important as genetic traits," adds Dr. McFarland.

MS twins are also participating in NINCDS therapeutic studies. In one protocol, white blood cells from a normal twin were removed by a process called leukopheresis. These cells were then infused into the twin with MS, in hopes of slowing down a suspected overactive immune response.

"Since the MS twin's condition became no worse," says Dr. McFarland, "this procedure may be worth pursuing in other MS patients."

The validity of experimental MS therapies, such as the leukopheresis performed on the twins, can be particularly difficult to interpret. Just as a patient's spontaneous remission can obscure the true effects of a treatment, so can environmental and emotional factors interfere with research analysis. MS symptoms often worsen after periods of activity, stress, fever, and exposure to heat. And the patient's anxiety or depression can cloud interpretation of a particular treatment's side effects.

"These factors don't produce a new attack of MS, but they can accentuate symptoms," says Dr. McFarland. "I once had a patient who had experienced optic neuritis—blurred vision—during an exacerbation. He recovered over a period of a few weeks and his vision returned to almost normal. But this fellow used to go out on evening walks. And what he found was that after he walked about a mile at a fairly brisk pace, he would start to get a recurrence of his visual difficulties. Now if he sat down and rested, his vision would return to normal over a period of minutes or hours. The exercise didn't produce a new attack of MS, but it produced enough physiological change in the body to make a lesion that was already there symptomatic."

The testing of experimental drugs on MS patients poses its own kinds of problems. A new drug, for example, that appears to help a patient with MS may actually have no value. Tests of certain drugs against placebos have shown that patients seem to improve under either treatment. This placebo effect is a common occurrence in MS patients.

Dr. McFarland is wary about the use of strong drugs in early-stage MS patients. "In the early years of MS, there is no way of telling which patients are going to have a mild course and which ones are going to have a severe course," he says. "Also, early in the disease, patients tend to get better anyway by themselves. For these two reasons, there is a reservation about using an experimental drug that has substantial side effects. The drug's risks must be balanced against possible benefits."

According to Dr. McFarland, if a patient has a severe course, drug side effects might be justified provided the drug also helps the patient in some way. "But, if the patient has only a mild course," he says, "it would be difficult to justify side effects such as increased risks of cancer."

The difficulties of evaluating drug treatments for MS were recently encountered by NINCDS grantee Dr. Howard L. Weiner of Brigham and Women's Hospital in Boston. As reported in *The New England Journal of Medicine,* January 18, 1983, his study tested high doses of cyclophosphamide, an immunosuppressant drug, on patients who had the chronic, progressive form of MS. The patients were also given ACTH, a hormone that stimulates the body to produce steroids. The results were mixed. The majority of patients given the two drugs stabilized or improved after six months and maintained that improvement for a year. Most of these patients, however, deteriorated two years later.

Dr. McFarlin, chief of the Neuroimmunology Branch, NINCDS, examines an MS patient while the patient's fraternal twin brother watches.

NIH PHOTO 1886

In an editorial in the same issue of *The New England Journal of Medicine*, in which Dr. McFarlin urged care in evaluating MS research, he described the results of the study as "interesting but preliminary . . . This experimental treatment should not be used routinely," he cautioned, noting that cyclophosphamide could cause major bladder complications or cancer.

Although the cyclophosphamide study is "promising," says Dr. McFarlin, more research is needed on this and other types of immunosuppressant therapy.

One day, Dr. McFarlin speculates, patients with a specific form of MS may be treated with a particular immunosuppressant drug—similar to the way patients with certain types of cancer are treated with specific anticancer drugs.

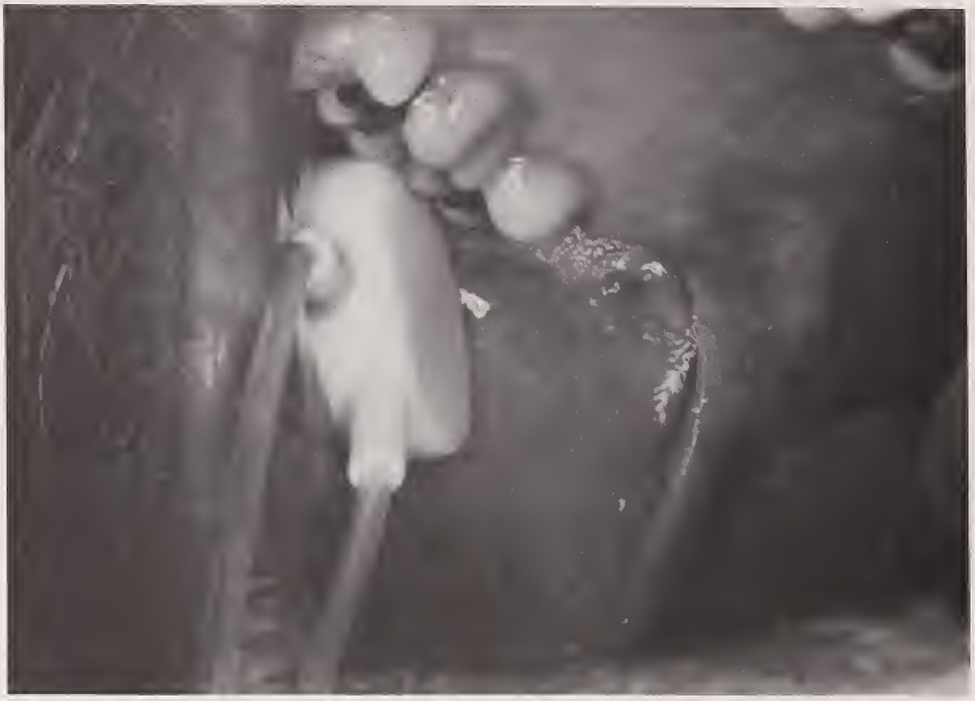
"Controlled studies of immunosuppression now under way may lead to the development of special protocols for different forms of MS," he predicts.

As far as his own research is concerned, Dr. McFarlin plans to conduct additional MS studies now that the Neuroimmunology Branch laboratory has relocated to the Clinical Center. "The move will enable us to expand our clinical research on multiple sclerosis and on other immunologically-based diseases of the central nervous system."

The Neuroimmunology Branch is looking for selected early-stage MS patients who would like to take part in long-term studies on the cause of the disease. Only a small number of patients are needed for therapeutic trials. The Branch is also looking for normal twins who would like to participate in research. These twins, who will serve as normal controls, will receive compensation for their efforts. Contact: Dr. Dale E. McFarlin or Dr. Henry F. McFarland, NINCDS, Building 10, Room 5B-16, Bethesda, MD. 20205. ■

Patients Suffering from Dry Mouth Now Seen in NIDR Clinic

Jody Dove



This instrument covers the opening of the duct from the parotid gland allowing the researcher to collect saliva from a single gland. NIH PHOTO 188

Do you feel the need to sip liquids frequently? Are you often thirsty? Does your mouth feel dry at night or upon awakening? Do you have trouble eating foods such as cereal or toast?

These are just some of the questions asked by Drs. Bruce Baum and Philip Fox of the National Institute of Dental Research (NIDR) in screening patients for their new dry mouth consultation service in the NIH Clinical Center.

Dr. Baum, clinical director and chief of NIDR's Clinical Investigations and Patient Care Branch, and Dr. Fox, an oral surgeon and staff scientist in the clinical investigations section, are seeking patients who have constant complaints of dry mouth and wish to be evaluated.

Dry mouth, also known as "xerostomia," is a common side effect of numerous medications or other therapies. It is also a symptom of certain diseases. Dry mouth is regarded as a significant health problem because it can affect nutrition, oral health, and psychological well-being.

When dry mouth occurs, it is associated with alterations in salivary gland function, either through a diminishing of saliva flow or qualitative changes in the saliva.

"Dry mouth conceivably represents a spectrum ranging from absolute shutdown of saliva to normal amounts of saliva with alterations in composition," explained Dr. Baum.

Saliva has several important functions: it cleanses the teeth of food particles; limits the growth of bacteria that contribute to the development of tooth decay (without sufficient saliva to provide a natural defense, extensive decay may rapidly develop which can lead to total destruction of the teeth); and preserves the teeth by bathing them with protective minerals such as calcium, phosphorus, and flouride.

Also, it moistens and lubricates the soft tissues that line the mouth and helps to keep them pliable; provides the moisture needed to stimulate the taste buds because taste sensations only occur when a substance in the mouth is dampened; and plays an important role in the digestive process by altering the consistency of food.

Patients who suffer from dry mouth experience varying degrees of discomfort. Some may observe only a dry or burning sensation. But in severe cases, cracking of the lips, slits at the corners of the mouth, changes in the surface of the tongue, and difficulty in eating, swallowing, tasting, and speaking may be reported.

"I've seen a number of patients who are depressed by the chronic nature of their symptoms. Having a dry mouth significantly affects their ability to taste and enjoy food. And with the current lack of effective treatment, even after the problem has been identified, it's a frustrating situation for both the patient and the doctor," observed Dr. Fox.

One of the most startling aspects found in examining the causes of xerostomia is that over 200 drugs list dry mouth as a side effect. These are drugs used quite commonly, and include antihypertensives, pain killers, sedatives, and even over-the-counter antihistamines. Anti-Parkinson's drugs such as artane have also been implicated.

Many of these drugs are frequently used by older persons. Although it is often assumed that altered saliva production and dry mouth occur as a result of normal aging, this is an incorrect generalization. Most dry mouth complaints in older patients are drug-related in origin.

Other causes of dry mouth are treatments such as radiation to the head and neck, chemotherapy, and bone marrow transplants; certain endocrine disorders; nutritional deficiencies such as anemia; and conditions such as anxiety, mental stress, and depression. Sjogren's syndrome, a connective tissue disorder, is also characterized by severe dry mouth.

Drs. Baum and Fox are particularly interested in cases of dry mouth in which the underlying causes are not clear.

All patients seen at the clinic will be evaluated to determine if there have been qualitative or quantitative changes in their saliva.

A goal of the current laboratory studies of Drs. Baum and Fox is to develop pharmacological regimens aimed at eliminating the specific underlying problem causing a patient's dry mouth.

Relief for dry mouth has typically consisted of using artificial saliva, available by prescription. Patients have also been encouraged to drink extra fluids or take frequent sips of water.

Practicing scrupulous oral hygiene by using fluoride gels, fluoride dentifrices, and dental floss daily has also been recommended to help circumvent severe dental problems.

In addition, to prevent mouth irritations, patients should avoid cigarettes, alcohol, and spicy, salty, and highly acidic foods.

Interested patients should have the dentist or physician call or address a let of referral to Dr. Bruce Baum, Bldg. 10, Rm. B1N107, NIDR, NIH, 9000 Rockville Pike, Bethesda, MD 20205 (301-496-1363). ■

Correct Diagnosis of Asperger's Syndrome May Improve Outlook for its Victims

Judy Folkenberg

Children who seem eccentric, aloof, and socially inept may be suffering from a relatively unknown clinical disorder called Asperger's syndrome which resembles (and often is misdiagnosed as) schizophrenia or autism.

Preliminary research now indicates that Asperger's syndrome probably is a developmental disorder, according to Dr. Digby Tantam of London's Maudsley Hospital.

At a recent seminar sponsored by the National Institute of Mental Health's (NIMH's) Division of Biometry and Epidemiology, Tantam presented findings from his research on the syndrome, and reviewed the work of the Austrian psychiatrist, Dr. Hans Asperger, who first described the syndrome.

Asperger published a paper on the syndrome in 1944 (he termed it "autistic psychopathy") but it remained largely unknown outside a small circle of German and Russian psychiatrists.

Asperger's patients were an unusual sample of children (average age 5-9), who came mostly from the Viennese intelligentsia.

He described his young patients as odd, "little adults" who lacked the ability to make social and emotional contact with others. In his words, "they were of the world but not in the world;" they had weird facial expressions, used didactic language, and always spoke as if addressing a public meeting. Most possessed at least normal intellectual abilities, and many had taught themselves to read.

Building on Asperger's description of the syndrome, Tantam further organized and clarified symptoms that characterize the disorder:

— Speech Patterns/Verbal Skills. Their speech tends to be pedantic and didactic, they have abnormal intonation patterns (voices are whiney or monotonous), and when speaking with others, they use the second or third person pronoun. Most cannot decode verbal cues. Language is almost entirely rote learned.

— Nonverbal Communication. Individuals use inappropriate gestures and lack facial expression. One of Tantam's patients looked away whenever Tantam spoke. They also lack the ability to interpret a speaker's facial expressions or gestures.

— Motor Coordination. Such persons are clumsy, and are poor at games involving motor skills.

— Social Competence. "They have no ability to understand and use rules governing social behavior; they have no common sense," says Tantam. The parents of one of Tantam's patients reported that they could not talk about their friends without their son repeating the conversation to the person in question.

— Intelligence/Eccentricities. While persons with this syndrome may be fairly intelligent, their intellectual range is narrow, their interests usually seem eccentric, and they often have learning problems in school. For example, they may show keen knowledge about the history of steam engines between 1860 and 1870 or have memorized the bus time-tables for the southern half of England but have no idea of the larger picture, or the frame of context in which they learn this information. Says Lorna Wing, a colleague of Tantam, "their special abilities are based mainly on rote memory, while comprehension of the underlying meaning is poor." "They handle well the kinds of things you can tell a computer—but they don't deal with concepts or ambiguity," adds Tantam. Patients can also be eccentric. One patient who was interested in time always wore two watches—one set at Greenwich Mean time and one set at local time.

While Asperger's syndrome can be regarded as a form of schizoid personality, its victims are not schizophrenic, according to Wing. "People with Asperger's syndrome do not experience such symptoms of schizophrenia as thought echo, voices commenting on their actions, or feelings that external forces are exerting control over their will, emotions, or behavior," she says.

In addition, there is a "marked contrast between the vague wooliness of schizophrenic thought and the concrete pedantic approach found in Asperger's syndrome," she says.

Nor should Asperger's syndrome be confused with early childhood autism. An autistic child is mute or has delayed speech, while a child with Asperger's syndrome uses good grammar and vocabulary, although the content of the speech is inappropriate for the social context.

Tantam studied 56 adults (most in their early 20s) who were identified by his psychiatric colleagues as eccentric and who had had a series of mental health and social problems. Based on personal interviews, interviews with their parents, personality and neurological tests, plus access to their case histories, Tantam made the diagnosis of Asperger's syndrome.

Most were males (a sex ratio in line with other developmental disorders) and lived with their parents. Approximately one-half needed remedial schooling, less than 20 percent were employed at the time of the study, and none had married or been engaged. A sizeable number had at one time been involuntarily admitted into a psychiatric institution. A large number also had been previously diagnosed as autistic or schizophrenic. Most exhibited the characteristics originally described by Asperger.

"A diagnosis of Asperger's syndrome is helpful," says Tantam, "because it enables parents to understand their child's condition and to take steps towards helping them." A parent who thinks of this as a handicap rather than a disorder can then take positive action towards managing the handicap."

With regard to employment, persons with Asperger's syndrome can hold down jobs as long as a sympathetic employer is aware of their eccentricities and a regular structured routine is maintained.

With regard to schooling, Wing stresses the importance of sensitive education. "The teacher has to find a compromise between, on the one hand, letting the child follow his own bent completely, and, on the other, insisting that he conform."

She adds that there is no kind of school particularly suited for children with Asperger's syndrome. Some have done well in schools for normal children, while others have managed better in schools for handicapped children.

As clinicians learn to distinguish Asperger's syndrome from schizophrenia, Tantam says, corrected diagnosis will keep psychiatrists from treating these individuals with neuroleptics (a drug commonly used for schizophrenia), "as it is not effective with these patients." ■

Major Accomplishments Cited at Diabetes Day

Linda Stalvey

In his opening remarks to Diabetes Day participants, Dr. Lester B. Salans, director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), noted that "There has been unprecedented accomplishment in basic research, as well as in clinical investigations in all aspects of diabetes that have provided both a theoretical and a practical basis for development of a broad range of therapeutic interventions . . ."

The program attended by about 250 physicians, diabetes educators, and nursing staff, was cosponsored by the Clinical Center, the Diabetes Branch, NIADDK, and the Washington D.C. area affiliate of the American Diabetes Association.

Major advances cited included progress in finding the causes of diabetes, both Type I or insulin-dependent diabetes mellitus (IDDM), and Type II or noninsulin-dependent diabetes mellitus (NIDDM); in defining the mechanism of action of insulin and other hormones, such as glucagon, somatostatin, and endorphins; in the explosion of knowledge in molecular biology that allowed for the isolation and use of genes to synthesize human insulin; in defining the relationship between metabolic control and development of diabetic complications; in establishing methods of diagnosis and assessment of treatment particularly the use of hemoglobin A_{1c}; and in improving methods of treatment.

The morning session was devoted to NIDDM, which accounts for 85 percent of the diabetes in this country. It is often characterized by normal or elevated plasma insulin levels, suggesting insulin resistance, a condition in which the body's physiological response to insulin is not proportionate to the circulating levels of the hormone. Dr. William G. Blakcard, Medical College of Virginia, spoke about the pathophysiology and treatment of NIDDM. He said that today, many diabetologists believe that insulin resistance, observed in obese as well as other diabetogenic states, may be the result of postreceptor defects.

A number of other studies have observed a reduced mass in beta cells in the pancreas of people with Type II diabetes. This defect may be inherited. Studies also suggest that many people with this type of diabetes have an abnormal insulin gene on the 11th chromosome, but it is unclear at present whether this abnormal gene is related to reduced beta cell mass or not.

Regardless of the causes of NIDDM, current forms of therapy include diet, exercise, and oral agents. Dr. James Anderson, University of Kentucky, addressed the nutritional options for diabetic patients, outlining high fat, high protein, high carbohydrate, and high fiber diets.

Dr. Anderson related his success in treating lean patients with a high carbohydrate, high fiber diet composed of 70 percent carbohydrate, 18 percent protein, 12 percent fat, and 65 grams of fiber. He stated that in 70 percent of lean patients treated, the insulin dose was initially reduced. Eventually, in 67 percent of those patients, insulin was discontinued. Cholesterol and triglycerides were also reduced in 30 percent and 14 percent of the patients, respectively.

Dr. Simeon I. Taylor, Diabetes Branch, NIADDK, discussed some unusual forms of NIDDM, stating that the entire disease is a poorly understood syndrome. Even the name tells us what it is not, rather than what it is. Over the past decade, however, disease mechanisms have been identified for a few unusual forms of NIDDM.

Dr. Taylor described three diverse diseases that are included under the diagnostic umbrella of NIDDM. Leprechaunism, which has been linked to a receptor defect, causes a failure in intrauterine growth. Babies who are born with the disorder are extremely small and have extreme insulin resistance. Most of these children die within the first few months of life. Lipoatrophic diabetes, whose defect is thought to be genetic, is marked by a distinct absence of body fat, the skin rash acanthosis nigricans, and striking masculinization of female patients.

A third type of NIDDM, type B extreme insulin resistant diabetes is autoimmune in nature. Patients also display acanthosis nigricans and masculinization in females. This overlap in clinical features has led to the speculation that hyperinsulinemia—a biochemical feature common to all these syndromes—may play a causal role in the pathogenesis of these features.

The afternoon meetings were devoted to Type I diabetes, or IDDM. Diabetes may result in long-term complications, which may involve every tissue in the body. The blood vessels, nervous system, kidneys, and eyes are particularly affected. While successful control of blood glucose levels may reduce the risk of complications, the exact relationship between these factors is not fully understood. The "glucose hypothesis" proposes that better physiologic control of blood glucose lessens the clinical complications of diabetes.

Dr. Charles M. Peterson, who led the afternoon sessions, is an associate professor at The Rockefeller University, lecturer at Mt. Sinai School of Medicine, and attending physician, Department of Medicine, New York Hospital. He addressed the relationship of glucose "control" to secondary manifestations or sequelae of diabetes from a biochemical approach.

A number of variables associated with hyperglycemia have been shown not only to be preventable, but also reversible if blood glucose levels are brought into the normal range. For example, abnormal

The Clinical Center nursing staff maintains a close relationship with diabetic patients in explaining the illness, the necessary medications, new techniques, and home care.

NIH PHOTO 1888

Patients now can accurately test glucose levels at home. The home glucose monitoring program can help patients measure and control the amount of glucose needed.

NIH PHOTO 1889

lipid profiles, early red cell senescence, abnormal white cell adherence, abnormal *in vitro* platelet aggregation, and abnormal fibrinogen kinetics all improve if glucose levels are normalized.

Dr. David Nathan, assistant professor of medicine at Harvard Medical School, and director of the Diabetes Clinic and Inpatients Diabetes Care at Massachusetts General Hospital, presented his overview and perspective on insulin pumps. Dr. Nathan began his talk by stating that "Since the 1921-1922 introduction of insulin we have done very little to help the clinical management of diabetes." Since mortality and morbidity have decreased with insulin therapy, other complications of diabetes, like cardio-renal-vascular changes have been revealed. Dr. Nathan maintained that the problem of metabolic control is dependent on the answers to two questions. Can control of glucose be measured and can tight control of glucose be attained?

The answer to the first question is "yes." With the advent of home glucose monitoring, patients can accurately test glucose levels at home. The measurement of hemoglobin A1c also provides a basis on which to judge glucose control over a long period of time.

The answer to the second question is also "yes," based on recent research, including work with insulin pumps. Dr. Nathan described "closed" and "open" loop pumps, and information gleaned from studies with both. The "closed" loop pump contains a built-in glucose sensor that dispenses insulin or glucose in response to the patient's need. In the "closed" loop method, the patient is connected to a large machine by two intravenous catheters. One catheter samples blood for glucose analysis. The glucose level is then fed into a computer, the appropriate dose of insulin is calculated, and then dispensed to the patient from a second catheter. This method is designed for short-term use in hospitalized patients.

The "open" loop system consists simply of a compact pump that delivers insulin through a subcutaneous catheter. This type of system is portable and can be used on an outpatient basis in conjunction with home blood glucose monitoring. Dr. Nathan stressed that insulin pumps are a very useful research device, and have been successful in very restricted research settings. Patients to date have been highly motivated, well educated to the process, and have had intensive staff supervision. Under these circumstances, tight blood glucose control, either with a pump or multiple daily insulin injections, has been achieved. He further stated that the answer to the question of whether or not tight blood glucose control makes a difference in preventing the long-term complications of the disease is not yet available. The Diabetes Control and Complications Trial, funded by NIADDK, has now begun to study this question.

The last speaker was Dr. Lois Jovanovic, who has joint appointments in both medicine and obstetrics and gynecology at Cornell University, and is also associate director of the Clinical Research Center at New York Hospital. She spoke of her experience in treating the pregnant diabetic woman.

Dr. Jovanovic expressed the opinion that when the insulin-dependent woman becomes pregnant, efforts to achieve normoglycemia must be considered as a standard of care. Dr. Jovanovic's studies defined normal blood glucose values for pregnant diabetic women, established a specific diet to assess insulin dose, and developed an appropriate insulin delivery system.

Dr. Jovanovic also established glucose and insulin requirements for women undergoing active labor. Looking at active labor as a stressful occurrence, she expected an increase in insulin requirements. In actuality, she found that no insulin is required during active labor, placing labor in an "exercise" category rather than a stress category.

Fifty-two patients delivered 53 healthy babies during this study—none delivered the very large baby common to diabetic mothers under poor glucose control.

Dr. Jesse Roth, chief, Diabetes Branch, NIADDK, summarized the highlights of Diabetes Day by recapping advances in the pathophysiology, diagnosis, and therapy of diabetes. He noted that recent advances in basic research have provided new and important insights into the mechanism of insulin action in the regulation of glucose transport. From the diagnostic viewpoint, he emphasized that both Types I and II diabetes seem to be a series of diseases. Physicians should look carefully at individual patients. This individualization could lead to a differential diagnosis of diabetes and perhaps to more effective therapy.

Finally, Dr. Roth urged the audience to remember non-drug methods of treatment for Type II diabetics. Diet and exercise should be given their appropriate place in importance, and other treatment should be used only when diet and exercise are not effective.

He closed by saying "The specialist is giving more information and guidance to the generalist, and the physician is turning more and more responsibility to the patient. This extension of expertise has reaped enormous benefit."

The future in diabetes research looks bright, and the hopes of the diabetic community were summed up by Dr. Salans' comment that it "will not be too far in the distant future that one will be able to take special steps to prevent certain types of . . . diabetes." ■

National Diabetes Advisory Board Releases Current Information for Physicians

Betsy Singer

By applying the most recent research and clinical findings, physicians can significantly reduce the incidence and severity of some of the complications of diabetes mellitus. The National Diabetes Advisory Board (NDAB), which advises Congress and the Department of Health and Human Services, has produced a guide for primary care practitioners. The guide represents a consensus among experts about treatment of five of the complications of diabetes: complications of pregnancy; kidney failure; diabetic retinopathy and visual impairment; acute ketoacidosis; and foot problems and amputations.

The guide is based on the most advanced treatment of diabetes, and national experts believe the application of these principles would improve the care of diabetics and reduce the high cost of hospitalization for complications of diabetes.

The Diabetes Mellitus Interagency Coordinating Committee (DMICC) recently sponsored a conference at the Uniformed Services University of the Health Sciences, in Bethesda, to introduce these recommendations to approximately 150 physicians from Federal agencies that provide direct care services or influence the health care system.

Dr. Charles M. Clark, Jr., director of the Diabetes Research and Training Center at Indiana University, chaired the NDAB workgroup that produced the guide. He also served as moderator for the DMICC conference. According to Dr. Clark, the guide focuses on generally accepted and established approaches to prevention and treatment on which there is agreement. The guide does not address one of the major unresolved issues in diabetes research—the role of the management of blood glucose per se in the prevention of the long-term complications of diabetes.

Dr. Ernest W. Johnson, chairman of the DMICC, and acting director of the Division of Diabetes, Endocrinology and Metabolic Diseases at NIH pointed out that the question of blood glucose control is the subject of a major clinical trial, sponsored by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK),

The clearest scientific evidence that tight control of blood glucose decreases some complications of the disease comes from investigations of diabetes in pregnant women. Studies in several countries "have shown conclusively that the high mortality and morbidity that threaten diabetic pregnancies can be reduced significantly by careful monitoring and intensive metabolic management," the guide says.

Mary Wells, R.N., explains an insulin pump to a diabetic patient.

NIH PHOTO 1890

About 10,000 babies per year are born to diabetic mothers, and another 60,000 to 90,000 are born to women who develop a temporary form of diabetes during pregnancy called gestational diabetes. The guide recommends: "Screening for gestational diabetes should be routinely incorporated into prenatal care. All pregnant women should have a blood glucose determination made between the 24th and 28th weeks of pregnancy."

Because the management of insulin-dependent diabetic pregnancies is so specialized, pregnant women with this type of diabetes should be treated at a major medical facility, if at all possible. Management consists of frequent and intensive attention to metabolic treatment, weight gain, blood pressure, renal function and fetal health.

According to Dr. Eli Friedman, chief nephrologist at Downstate Medical Center, Brooklyn, New York, the kidneys of about one in four U.S. dialysis patients fail due to diabetic nephropathy. Although controlling hyperglycemia has not been proven to delay damage to the kidneys, the guide suggests that physicians inform their patients of the possible benefits of controlling both their blood glucose levels and hypertension, avoiding drugs that damage the kidneys, and controlling kidney infections. According to the guide, however, when kidney failure is complete, "current data suggest that renal transplantation is most successful in patients with diabetes when performed early."

Diabetes is a major cause of blindness in the U.S. About 5,000 new cases of blindness related to diabetes are reported each year. When patients have suffered from diabetes for about 15 years, more than 80 percent develop some retinopathy, although usually it does not seem to affect vision. In a small group of patients with diabetes, retinopathy progresses to proliferative retinopathy, which does threaten eyesight.

According to Dr. Paul Palmberg, an ophthalmologist from the University of Miami who participated in the conference, ophthalmologists have been able to prevent more than 60 percent of blindness caused by bleeding of the newly proliferating vessels into the vitreous chambers of the eye by using laser coagulation therapy. Because of the effectiveness of this treatment, detection of the first signs of proliferative retinopathy is important. Thus, the guide recommends that primary care physicians refer patients with diabetes to ophthalmologists, unless the primary care physician has a high degree of experience in the diagnosis and evaluation of diabetic retinopathy. The guide also suggests that physicians refer Type I (insulin-dependent) diabetic patients to ophthalmologists five years after diagnosis of diabetes, and that Type II patients (noninsulin-dependent) be referred at the time of diagnosis, because often diabetes has been present for several years before diagnosis.

In Type I diabetes, patient adherence to the treatment regimen is especially important for preventing diabetic ketoacidosis (DKA). DKA and the acute metabolic decompensation that precedes it are severe, but often preventable, complications of diabetes caused by an insufficient level of circulating insulin. The initial phases are recognizable, and treatment can often prevent further progression. Approximately 14 percent of patients with Type I diabetes are hospitalized each year with DKA. Among diabetic patients under age 19, 60 percent of all hospital admissions are due to DKA.

Many patients do not follow the advice of physicians because the patients' health beliefs conflict with what the physician tells them. For example, the patient may not believe the diagnosis or that the treatment will be effective. Physicians can improve patient adherence by discussing individual health beliefs, providing patient information and encouraging patients to participate in their own care, the guide suggests.

"You can change patients' attitudes about their susceptibility, the seriousness of the disease, and the benefit of following your advice," according to Dr. Marshall H. Becker, expert in patient adherence at the University of Michigan School of Medicine, Ann Arbor. He suggested that physicians simplify their instructions to patients, highlight the most important principles, avoid jargon and avoid scare tactics. "Cater to motives other than fear," he says.

The guide contains information pages about each of the five complications and suggests that these be photocopied and given to patients. "One handout, a sick day guide, is especially helpful because it gives diabetic patients advice about monitoring various signs so that they can give detailed information to their physician over the phone or when they go to the office," says Dr. Karl Sussman, chief of Endocrinology, Veterans Administration Hospital, Denver. "These patient handouts help patients learn the principles of self-monitoring. Getting patients involved in their own care improves adherence," he says.

For example, preventing damage to the feet and amputation are complications for which patient education may be the most important tool. A study at Emory University showed that patient education helped to decrease by 50 percent the number of foot amputations due to diabetes. The guide's patient-education handout, written for laymen, recommends that patients examine their feet daily, stop smoking and wear comfortable, soft leather shoes.

In summary, Dr. Clark said, "This is the first attempt by the specialists who deal with diabetes, including ophthalmologists, and nephrologists, to offer physicians specific and practical guidelines for treating diabetic patients. It emphasizes the importance of involving patients in their care and their collaboration with primary care physicians and specialists." Research in diabetes and in education show that this approach can significantly improve care for patients, he says.

Initially, the guide is being disseminated to physicians and other health professionals through established programs for continuing education in diabetes. These programs include the Diabetes Research and Training Centers of the NIADDK, the National Diabetes Control Program of the Centers for Disease Control, and Federal agencies with direct health care delivery programs. ■

Antiviral Agent May Be Life-Saving for Certain Herpes Zoster Patients

Patricia Randall

Vidarabine, a drug used to treat patients with herpes virus encephalitis, can also prevent the life-threatening complications of herpes zoster in immunocompromised patients, according to studies supported by the National Institute of Allergy and Infectious Diseases (NIAID). The Food and Drug Administration recently announced approval of this new use of the drug.

Although the number of patients who may benefit from this treatment is small, Dr. Richard M. Krause, director of NIAID, stressed the importance of vidarabine as a life-saving drug and as a pioneer product in the long search for drugs effective against viral infections. Earlier NIAID-supported studies led to the initial approval of vidarabine as the first injectable drug for treatment of patients with a serious viral infection.

Herpes zoster, also called shingles, is caused by reactivation of the chickenpox virus and occurs in 10 percent of the population, usually after age 50. It produces a blistery rash on the skin and pain that sometimes persists for several weeks after the lesions have healed (postherpetic neuralgia). Although uncomfortable, herpes zoster is not life-threatening for most people.

However, in persons whose immune systems are affected by underlying disease or by treatments with anticancer drugs, herpes zoster can spread from the skin to vital organs of the body and may cause death. Until now, there has been no effective treatment for the disease.

In the NIAID-supported study, physicians administered either vidarabine or a placebo to immunocompromised patients within 72 hours after they developed herpes zoster. The drug or placebo was given intravenously over a 12-hour period on five consecutive days. Neither patients nor physicians knew which substance was being given. Only five percent of 63 vidarabine-treated patients with herpes skin lesions developed zoster-related systemic complications, compared to 19 percent of the 58 placebo-treated patients.

Vidarabine accelerated healing of the skin lesions and decreased the frequency of lesion spread to other skin areas. Lesion spread occurred in 24 percent of untreated patients and in only eight percent of treated patients. Treatment also reduced the length of time patients suffered postherpetic neuralgia. Four months after the onset of the infection, 56 percent of the treated patients were free of pain, compared to only 17 percent of untreated patients.

Physicians noted that patients with lymphoproliferative cancers and those 38 years of age or older were at greatest risk for complications of herpes zoster, and they also benefited most from therapy. None of the patients suffered serious side effects.

This study was done as part of an ongoing NIAID-sponsored program at collaborating medical research centers throughout th country to test antiviral substances.

The study was reported in the *New England Journal of Medicine* by Dr. Richard Whitley and colleagues. It was supported by a contract from NIAID, by grants from the National Cancer Institute and from the General Clinical Research Centers Programs, NIH, and by the Robert Meyer Foundation. ■

Tardive Dyskinesia: A Side Effect of Neuroleptic Drugs Evaluated at NIMH Meeting

Marilyn Sargent

The 14-year-old boy stood rigidly before the camera while being taped. His head moved to one side and back over and over again. Simultaneously, his mouth opened and closed in a continuous and rhythmic fashion. He appeared to be trying to swallow something that refused to go down.

The youngster was one of several developmentally disabled patients who appeared on a tape shown to researchers describing a condition known as tardive dyskinesia.

The investigators were attending a meeting, organized by the Pharmacologic and Somatic Treatments Research Branch (PSTRB), National Institute of Mental Health (NIMH), to bring together for the first time experts on tardive dyskinesia in two populations: the psychiatrically disordered and the developmentally disabled.

Tardive dyskinesia is a condition manifested by involuntary, repetitive movements—most often of the tongue, mouth, and face, but extending to other parts of the body in some cases. It occurs in some individuals—estimates range from 5 to more than 50 percent—who have been treated with neuroleptic drugs, a class of psychoactive medications used for such psychiatric and neurological disorders as schizophrenia, mental retardation, autism, Tourette's syndrome, and Huntington's disease.

The videotapes of the developmentally disabled youngsters were shown to the researchers by Dr. Thomas Gualtieri, School of Medicine, University of North Carolina, who asked them to diagnose the youngsters' conditions without knowledge of the patients' histories. He admitted that the cases were particularly challenging in terms of differentiating movements caused by tardive dyskinesia from movements associated with other disorders.

For example, many mentally retarded and autistic individuals manifest strange and repetitive movements referred to as stereotypies. Also dyskinesias can be caused by illness, brain damage, or other neurological conditions.

The discussion ensuing from the tape centered on the dilemmas that face clinicians who treat psychiatrically and developmentally disabled patients, dilemmas complicated by the unnecessary use of neuroleptics for many patients, for long durations, and at unnecessarily high doses, according to the scientists.

Among the dilemmas is the double-edged action of the drugs themselves. While neuroleptics can cause dyskinesia, they also can ameliorate both drug- and non-drug related dyskinesias in many patients, leading to a vicious cycle: the dyskinesia is treated with a neuroleptic, which eventually causes the reappearance of dyskinesia, which is then treated with increased doses or another neuroleptic, which eventually causes the return of dyskinesia.

Nevertheless, neuroleptics remain the treatment of choice for schizophrenia. They diminish hallucinations, delusions, and bizarre behaviors, freeing many patients from institutional life. For the developmentally disabled, neuroleptics may control self-destructive and aggressive behaviors as well as stereotypies.

Unfortunately, the characteristics which make neuroleptics useful also make them vulnerable to misuse, said Dr. Robert Sprague, Institute for Child Development, University of Illinois, referring to a number of malpractice suits relating to tardive dyskinesia.

To protect physicians from possible lawsuits and their patients from tardive dyskinesia, the researchers agreed, clinicians and heads of inpatient facilities should ensure that their patients' movements are monitored before and during drug treatment as well as during periods following drug withdrawal. Such monitoring helps to differentiate tardive dyskinesia from other dyskinesias and from stereotypies in most patients. Further, they said, monitoring patients following drug withdrawal helps differentiate patients who need drug treatment from those who are better off without them.

A number of techniques are available to help trained observers monitor the movements associated with tardive dyskinesia. One technique developed by NIMH researchers called Abnormal Involuntary Movement Scale (AIMS), was discussed by Dr. Nina Schooler, PSTRB, who noted that systematic examination procedures and standardized rating scales are prerequisites to diagnosing tardive dyskinesia. A one-time observation can, at best, identify a "presumable" dyskinesia, she said. According to the Research Diagnoses for Tardive Dyskinesia (RD-TD) developed by Schooler and Dr. John Kane, Long Island Jewish Hillside Hospital, an AIMS rating of either mild abnormal involuntary movements in two body parts or moderate movements in one body part is criterion for a diagnosis of dyskinesia.

Joanne Severe, an NIMH statistician, discussed a computerized data form produced by PSTRB to record information required for obtaining a diagnosis of tardive dyskinesia. Called Modular Algorithm for Tardive Dyskinesia Diagnosis (MALTD), the form can be used with any monitoring and rating system.

Dr. Jonathan Cole, McLean Hospital, Boston, and Dr. James Smith, Hudson River Psychiatric Center, Poughkeepsie, New York, both used AIMS to study psychiatric populations. They found no clear pattern for either onset of tardive dyskinesia or remission following drug withdrawal. As Cole pointed out, "some patients felt better, some stayed the same, and still others did not feel better when taken off medication." Both investigators expressed disappointment about the amelioration of tardive dyskinesia following drug withdrawal.

Dr. Smith, who found females had more severe forms of the disorder, also pointed out that age also affects its persistence. Older, chronic schizophrenics show no improvement even after taking no medications for three years.

In contrast, Dr. Stephen Breuning, Western Psychiatric Institute and Clinic, reported that among the developmentally disabled many individuals withdrawn from drugs show major improvements after four months.

Bruening mentioned studies that he and Dr. Gualtieri carried out, and found "amazingly similar results," considering they had no previous knowledge of each other's research."

Both researchers found dyskinesia in about 33 percent of their subjects. The presence of the disorder was related to duration of drug exposure. Following drug withdrawal, abnormal movements and behavioral problems occurred in 34 percent of both study populations. The prevalence of moderate to severe symptoms increased during the first four weeks and then diminished, dropping dramatically by 15 or 16 weeks.

Getting patients and those who care for them through the "four months of agony" that follow drug withdrawal is a major problem, said Breuning. Noting that such suffering could be reduced if drugs we given only when absolutely necessary and at minimal doses, he suggested that appropriate behavioral techniques could dramatically reduce the need for drugs.

"With a strong behavioral program, only 20 percent of patients would need medication, and even without a strong program, only 30 percent would need drugs," he estimated.

Behavioral intervention offers other advantages, Breuning added. It is effective with non-drug responders and also differentiated tardive dyskinesia from stereotypies. For example, stereotypies will stop if a patient is distracted by a toy or conversation, but the tardive dyskinesia movements continue, he explained.

Dr. John Kane, who carried out the first prospective study of tardive dyskinesia in 800 patients with all types of psychiatric diagnoses, said he did not see the same dramatic increase in symptoms following drug withdrawal in the mentally ill population that Breuning reported in the developmentally disabled.

He found 12 percent of his population developed tardive dyskinesia over a 4-year period. Most of his subjects had been on medication for less than a year at the start of the study.

Kane's findings, corroborated by others at the meeting, also did not support past suggestions that certain drugs, such as Mellaril (thioridazine), caused less tardive dyskinesia.

Cole pointed out that biological variability in patients appears to play an important role in vulnerability to tardive dyskinesia. Some patients get tardive dyskinesia after very short exposure to drugs, he noted. "My guess is that if you studied 3,000 patients, well-documented findings would indicate that the type of drug will be less important than patient vulnerability in determining risk for tardive dyskinesia."

In summarizing the 2-day meeting, Dr. Arnold Friedhoff, Millhauser Laboratories, NYU School of Medicine, pointed out that the definition of tardive dyskinesia may need revision in that drugs other than neuroleptics have been found to cause similar movements. Also, the variety of dyskinesias—withdrawal, illness-related—make it a confusing term.

When discussing future research needs, Friedhoff suggested further studies on specific factors that place individuals at risk for tardive dyskinesia. Women and older people appear to be particularly vulnerable, and there is evidence to associate duration and dosage of medication with severity, but there are enough differences in outcome to warrant more studies, he said. "Some people get better while on drugs, and some just stay the same. Not everyone gets worse," he pointed out.

A major concern of the researchers was the need to educate clinicians and superintendents of institutions, particularly for the developmentally disabled, about appropriate use of medication and behavioral procedures so as to cut back both the numbers of those treated with drugs and the dosages used to treat those who require medication.

For further information contact Dr. Nina Schooler or Natalie Reatig, PSTRB, 5600 Fishers Lane, Rm. 10C-06, Rockville, MD. 20857. ■

Amniotic Fluid Can Help Save the Lives of Premature Babies

Tineke Bodde'

A new procedure for treating premature infants with respiratory distress syndrome (RDS) is being tested by researchers supported by the National Institute of Child Health and Human Development (NICHD). Healthy 9-month-pregnant women undergoing cesarean childbirth have helped save the lives of other mothers' premature babies by donating their amniotic fluid which contains a beneficial lung lubricant called "surfactant."

The procedure, so far used on eight very premature infants, was developed through research conducted at the University of California Medical School in San Diego. Details of the research were presented at the 1983 joint meeting of the American Pediatric Society, the Society for Pediatric Research, and the Ambulatory Pediatric Association in Washington, May 4.

After successfully treating premature animals with the human surfactant, Drs. Louis Gluck, Mikko Hallman and T. Allen Merritt found that purified lung surfactant collected from human amniotic fluid and placed into the tracheas of human neonates suffering from RDS significantly improved their breathing. The infants weighed less than 1200 grams (approximatley 2½ pounds) and were treated within 10 hours after birth.

Surfactant is an emulsifying substance produced by the fetus largely after the 35th week of gestation. It helps inflate the alveoli (air sacs) in a baby's lungs after birth and prevents the tiny sacs from collapsing and sticking together after each breath.

RDS is a common and often fatal condition affecting very premature infants who have not yet produced enough surfactant. It has been estimated that RDS and its complications account for as many as 8,000 to 10,000 neonatal deaths among live born infants per year in the United States and affects some 40,000 newborns annually.

In NICHD's prospective controlled trials, conducted at the Infant Special Care Unit in San Diego, Dr. Gluck and his team treated eight very low birth weight infants who suffered from severe RDS. The human surfactant was deposited in the infants' tracheas via a tube inserted through the mouth some six hours after birth while the infants received mechanical ventilation. A group of 17 low birth weight infants with severe RDS, receiving mechanical ventilation only, served as controls.

X-rays and blood gas analyses showed that within minutes, respiration of the eight surfactant-treated infants improved considerably, compared to that of the newborns receiving conventional mechanical ventilation without surfactant. "The beauty of natural surfactant is that it increases oxygenation to the infants so that we can reduce mechanical ventilation, and give less oxygen," said Dr. Gluck. Under certain conditions oxygen therapy, while life saving, may cause eye and brain damage.

In a process developed by Dr. Hallman, the natural surfactant had been isolated from the amniotic fluid of full-term mothers during cesarean section after lung maturity of the mothers' own babies had been confirmed. According to Dr. Gluck, "Out of four cesarean sections we can collect enough surfactant to treat one baby with respiratory distress. The isolation technique is relatively inexpensive."

According to Dr. Sumner J. Yaffe, director of NICHD's Center for Research for Mothers and Children, "It is essential that further studies evaluate the effectiveness and safety of the human surfactant treatment before these findings are translated into widespread clinical usage. It is hoped that this new development in fetal medicine will bring a further reduction in this country's infant mortality rate which in 1982 was 11.2 deaths per 1,000 live births." ■

Kidney Involvement in Lupus Studied at NIADDK

Barbara Weldon

More than half a million American patients are awaiting a cure for a mysterious, potentially fatal, connective tissue disorder known as systemic lupus erythematosus (lupus).

Lupus is primarily a disease of young adults, which strikes an estimated 50,000 people each year. Almost 90 percent of its victims are young women of childbearing age. The disease, a disorder of the body's immune system, may affect the kidneys, heart, lungs, or central nervous system.

Over the past 30 years, more than 1,000 patients with lupus have participated in a research program at the NIH's Clinical Center. Research scientists at the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), are dedicated to trying to find a cure for the disease.

The major thrust of their program has been research on the effect lupus has on the kidney, and how best to treat this major complication of the disease. According to Dr. John Klippel, a senior investigator in the Arthritis and Rheumatism Branch, "At one time, lupus was thought to be fatal, but now we know that in most cases it is a chronic disease."

Klippel said certain symptoms make a doctor think of lupus. These include arthritis, blood disease, kidney disease, sensitivity to the sun, or a persistent rash on the nose and cheeks. In about 20 percent of the cases, the lupus patient may have a false-positive reaction to a premarital test for syphilis.

Since lupus is a life-long disease that has no cure, many people ask how they can be admitted into a study program at the NIH.

To be accepted into the program, a patient must have a positive diagnosis of lupus and be referred by their physician. The researcher studying the disease will then evaluate the case to see if the patient fits into a particular research study. If patients are accepted, they are then divided into two groups based on the severity of their case. Patients with mild disease are treated in the outpatient clinic while those with more advanced disease are admitted as inpatients to the Clinical Center.

Once the patient is admitted to the hospital, a complete history is taken and laboratory studies are done. For example, a blood count is ordered to learn if the patient has too few red cells, white cells, or platelets (blood cells that control clotting). These blood tests also include an examination for a particular type of white cell (LE cell) often found in lupus patients, and an antinuclear antibody (ANA) test, which will determine if the patient has an unusual type of protein substance (antibody), found in many patients with autoimmune diseases like arthritis or lupus.

In other tests, researchers collect all urine passed in a 24-hour period to see if the kidneys are functioning properly. They do a chest X-ray to see whether the lungs are involved, and an electrocardiogram to see if the disease has affected the heart.

Since lupus differs in each patient, some treatments that work for one patient may not work for another. Therefore, NIADDK researchers are evaluating three distinct types of therapy to treat patients with kidney problems resulting from lupus. Researchers may give a specific type of immunosuppressive drug to stop lupus patients from producing too many antibodies (disease fighters). They may also combine several immunosuppressive drugs. In addition, they may vary the timing of the drugs, for example, giving large doses of immunosuppressive drugs early in the disease and then give them less frequently later on.

Most lupus patients are treated with steroids (prednisone and other agents). Researchers are convinced that these agents have reduced mortality and prolonged life in lupus patients.

Since death rates are highest in patients with kidney involvement, the primary focus of the research program is now the kidney, but other aspects of lupus continue to be studied. For instance, researchers have evaluated a procedure called plasmapheresis, in which the patient's blood is filtered through a machine that works like a cream separator. As the blood is withdrawn from the patient, it is spun rapidly with the heavier red cells separating from the plasma (liquid part of the blood containing antibodies). These antibodies are filtered out and discarded. The "cleansed" blood is then returned to the patient.

Another study is concerned with the genetic characteristics of lupus. Researchers recently studied eight families to determine whether inheritance contributes to the disease. Their studies included patients with lupus, their spouses, and immediate "blood relatives." They questioned patients about drug intake, nature of household contacts, and signs or symptoms of lupus. They then drew blood samples from each family member for evaluation. We find that "about 90 percent of patients have no family history of lupus. Almost 10 percent have family members with the disease," said Dr. Klippel.

Much of the current research on lupus at NIADDK focuses on the immune system and the role of antigens (substances that provoke the disease immune response) and antibodies (which are produced in response). Replacement of deficient cell material may be a possible treatment for lupus in the future.

Gene splicing and gene transfer are new, rapidly expanding research fields. If the patient is shown to have a genetic problem, such as a mutation in the chromosome, then scientists may eventually be able to delete the gene responsible for lupus and reinsert the correct gene to replace the defective one.

"We have to realize that we are dealing with a chronic disease and may have to follow the patient for years. One of the strengths of this program has been the excellent follow-up of lupus patients. This allows you to see the whole spectrum of the disease," said Dr. Klippel. ■

Firearms: The Most Common Method of Suicide

Judy Folkenberg

The use of firearms to commit suicide has increased dramatically over the past 25 years—according to Dr. Jeffrey H. Boyd in a recent issue of the *New England Journal of Medicine*.

In fact, "the rate of suicide by firearms has been increasing more than twice as rapidly as the rate of suicide by gas or poisoning," says Boyd.

Analyzing data on the numbers and types of suicides for the years 1953 through 1978, Boyd discovered that for individuals under the age of 40, the suicide rate rose much more rapidly—4.5 percent in 1953 to 9.3 percent in 1978. This dramatic increase was accompanied by a gunshot suicide rate which rose from 4.9 percent in 1953 to 7.1 percent in 1978.

During the same 25 years, the nonfirearm suicide rate did not change.

Interestingly enough, the number of guns in U.S. households has also increased. In an interview, Boyd said, that data from the Bureau of Alcohol, Tobacco, and Firearms, "showed that there were 51 guns per 100 persons in 1968 as compared to 73 per 100 in 1978."

Boyd notes that other studies have shown that handguns (as opposed to rifles) account for 83 percent of all suicides by firearms. Perhaps, Boyd suggests, the increase in suicide might be controlled by restricting the sale of handguns—for instance, instituting a waiting period between the intention to purchase a handgun and the actual purchase.

"I think," said Boyd, "that people who are depressed and/or alcoholic are also inclined to be impulsive. If it became more difficult for them to kill themselves—the impulse might pass."

Boyd also noted that another study shows that several states with very strict gun control laws have lower suicide rates.

In Britain, a decrease in the carbon monoxide content of domestic gas (gas, rather than firearms being the most common means of suicide) resulted in decline in the suicide rate.

But since one out of every six persons who is depressed commits suicide, sound medical practice includes, "getting guns out of the house of despondent people." ■

Science Writers Briefed on the Latest Progress in Digestive Diseases Research

Bobbi Bennett

The progress that is being made in defining the immunological defects and improving the treatment of various digestive diseases was the subject of a recent NIH Science Writers' Seminar.

The moderator, Dr. Jerry D. Gardner, chief, Digestive Diseases Branch, NIADDK, described the substantial economic burden of the spectrum of these diseases which cost Americans $17 billion a year for direct medical care. Digestive diseases are also the leading cause of hospitalization and major surgery in the U.S.

Dr. Warren Strober, chief, Mucosal Immunity Section, Laboratory of Clinical Investigation, NIAID, discussed the headway that he and others are making in identifying the cause of Crohn's disease, a chronic inflammatory disease of the intestine. Currently, Crohn's disease is thought to be caused by an abnormal and uncontrolled immune response. One hypothesis is that the error involves the suppressor T cells, the white blood cells that normally prevent the GI tract from mounting unwanted immune reactions against the enormous array of substances that pass through it.

Dr. Strober and Dr. Stephen James have found an increased number of certain kinds of suppressor T cells in the blood of patients with Crohn's disease. This increase in the circulation is accompanied by a notable lack of these suppressor T cells on the GI lesions of these patients. This suggests that the suppressor T cells in the GI lesions of these mucosa as they do in normal individuals and, as a result, unrestricted immune responses occur against ingested antigens, resulting in the chronic inflammation. Identification of the specific cellular abnormalities in Crohn's disease will enable scientists to develop more specific and effective therapies for controlling the course of this disease.

Dr. Robert T. Jensen, senior investigator, Digestive Diseases Branch, NIADDK, described his trials of drugs to control gastric acid levels in patients with Zollinger-Ellison syndrome (ZE). This disease is characterized by severe recurrent peptic ulcers due to the production of 10 to 25 times the normal amounts of gastric acid. This overproduction is a result of the release of the GI hormone gastrin by an islet cell tumor.

He has found that the gastric acid hypersecretion in these patients can be reduced by high doses of cimetidine—a drug which acts by blocking the interaction of histamine with its receptors on the parietal cells that secrete gastric acid. However, half of the males on the drug developed impotence or breast changes (enlargement or tenderness). Dr. Jensen recently published a report that ranitidine, a new drug in the same class as cimetidine but three times as potent, was also effective in the male patients but did not produce these side effects.

The DD group will soon be starting a trial of another drug in the same class as cimetidine but which is 50 to 100 times as potent, does not cause the anti-androgen side effects, and does not interfere with the metabolism of other drugs, another of cimetidine's problems. They will also be the first U.S. laboratory to evaluate one of the substituted benzimidazoles—a class of drugs that do not act upon the parietal cell's receptors but rather block the ability of the cell to release gastric acid. If long-term toxicity data show this extremely potent agent to be safe, it could become the drug of choice for ZE patients.

The status of research on primary biliary cirrhosis (PBC) was presented by Dr. Stephen P. James, an investigator in NIAID's Mucosal Immunity Section. This autoimmune disease, which predominantly affects middle-aged women, is characterized by inflammation and destruction of the bile ducts within the liver.

Dr. James is investigating the autoimmune nature of this disease in which the immune system may also attack the tear and salivary glands, thyroid, skin, and joints. He has found that patients with PBC have an increased number of antibody-producing B cells, and a defect in the function of their suppressor T cells. The decreased suppressor function could lead to the hyperactivity of the B cells, resulting in an overproduction of the autoantibodies that occur in this disease. He feels that this basic immunoregulatory abnormality could provide the background for other kinds of factors to cause the specific disease process.

If scientists could find factors that activate suppressor T cells, we would have a more effective treatment for this disease than the currently used anti-inflammatory drugs which, for the most part, are not very successful.

Dr. Jay H. Hoofnagle, senior investigator, Liver Diseases Section, Digestive Diseases Branch, NIADDK, discussed current efforts to find effective agents for treating chronic hepatitis B, also known as the hepatitis B surface antigen (HBsAg) carrier state. This condition—in which the person may be free of symptoms but the liver remains inflamed and the virus persists in the body—is probably the single most important cause of cirrhosis and liver cancer in the world. The new hepatitis B vaccine is useless for the five percent of the world's population who already have the HBsAg carrier state.

Dr. Hoofnagle's group conducted trials of recombinant DNA-produced interferon—a substance normally made by the body in response to a viral infection that prevents the virus from infecting other cells. They found that high doses did reduce the level of hepatitis B virus in the patients' blood but that when the interferon was stopped, the virus returned to its pretreatment levels. Similarly, a trial of the antiviral drug, adenine arabinoside monophosphate (ara-AMP), caused only a transient improvement in the chronic hepatitis B infection.

However, Dr. Hoofnagle found that when patients who had been treated with corticosteroids for their chronic hepatitis were withdrawn from them prior to starting the antiviral trials, many of them developed a spontaneous worsening of the disease, followed by long-term improvement. It appeared that the withdrawal of these patients from the immunosuppressive corticosteroids induced an overactivity of the immune system, and, with that, an acute hepatitis which eradicated the persistent viral infection in the liver. Encouraged by this observation, they have started a controlled trial to see how effective this form of immune manipulation will be in eradicating the HBsAg state. ■

MEDICAL CAPSULES

Sandra D. Levine

- The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is sponsoring a 21-center cooperative clinical study to determine if precise blood sugar control can help prevent the serious, long-term complications of diabetes. These can include blindness, cardiovascular and kidney disease, and nerve tissue damage.

In the phase of the Diabetes Control and Complications Trial (DCCT) now beginning, 252 volunteers with insulin-dependent diabetes will participate in studies aimed at determining whether a large-scale, long-term clinical trial would be feasible. If this initial two-year phase demonstrates that a larger scale study would be productive, a 7 to 10-year clinical trial involving many more patients will be conducted through the same medical centers.

Volunteers will be randomly assigned to one of two groups. Those in the "standard" treatment group will receive one or two insulin injections per day; a specialized meal plan; urine testing; an education program for self-management of diabetes; and routine checkups every three months. Participants assigned to the "experimental" treatment group will receive insulin either by injection three or four times a day or continuously by insulin pump; a specialized meal plan; self-monitoring of blood glucose levels; an education program for self-management of diabetes; an initial hospital stay; and checkups once a month.

To participate in the DCCT, a person must be between the ages of 13 and 39, have had insulin-dependent diabetes for at least one year but not more than 15 years, not have any severe complications of diabetes, be free of other medical or psychological problems that would make it difficult or unsafe to participate, be willing to fulfill study responsibilities, and live close enough to one of the DCCT medical centers so that appointments can be easily kept.

Further information on the DCCT and a list of participating centers can be obtained by calling (301) 496-3583, or writing to DIABETES, NIADDK, Building 31, Room 9A04, Bethesda, MD. 20205.

- Under a grant from the National Institute of Dental Research (NIDR), scientists are developing a liner for dentures that will be comfortable, impermeable to fluids, and strong enough to withstand the forces of chewing.

A liner is used to facilitate better denture fit when changes in the jaw bone cause a loosening of the denture. Currently available liners have not been satisfactory, but now scientists have formulated a new material by modifying an elastic polyphosphazine polymer called PNF.

Testing indicates that this new material does not allow fluids to penetrate, its texture can be adjusted to adapt to clinical requirements, and it bonds firmly to the denture base. More comfortable and durable dentures could result.

- The Division of Research Resources (DRR) has awarded a four-year grant to the University of Texas Health Science Center in San Antonio for the operation of a General Clinical Research Center (GCRC) at the Audie L. Murphy Memorial Veterans Hospital.

GCRCs offer scientists opportunities to study specific conditions and develop improved methods of treatment. Established by NIH in 1960, there are 74 GCRCs currently in existence at medical centers throughout the country. The San Antonio unit is the first to be located in a VA hospital.

About 30 treatment protocols have been approved for the new center, including evaluation of drug therapy for cancer, cardiovascular, neuromuscular, liver and kidney diseases.

- Scientists in the National Caries Program at NIDR are investigating the use of palatinose, a semi-sweet sugar derivative, as a sugar substitute in certain foods and medications.

Studies using palatinose in combination with saccharin or aspartame indicate that it would make a suitable sugar replacement because it inhibits glucosyltransferase, the enzyme thought to be involved in dental plaque formation, and therefore does not cause tooth decay.

- A new method of administering measles vaccine, by inhaling, appears to be effective.

In a clinical trial conducted by Dr. Albert Sabin and funded in part by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the undiluted, aerosolized vaccine was administered to 160 children in Mexico. The purpose of the study was to determine whether this method would be more practical than the currently available method in eliminating measles in countries where control is difficult.

Administration of the vaccine appeared to be effective also in infants with high levels of maternal antibody who cannot be immunized by conventional subcutaneous injection.

Since the vaccine is administered by a simple nebulizer, it could provide an efficient and economical means for controlling measles worldwide through mass vaccination programs.

Results of the trial were reported in the May 20, 1983 issue of *JAMA*.

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

Ms. Maureen Napper
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Building 31, Rm. 2B-10
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News&Features from NIH

July 1983

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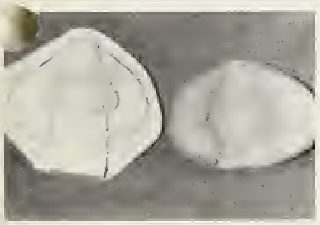
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

News&Features from NIH

July 1983

Patients undergoing radiation therapy for head and neck tumors can now receive treatment directly to the tumor with minimal exposure to the adjacent normal tissue through the use of the external-mold bite device.

Designed by scientists at the National Cancer Institute and the National Institute of Dental Research the acrylic device is individually constructed to fit over the patient's tumor. It contains radioactive metallic seeds and is worn for a few hours each day for three weeks. The patient must remain in an isolated hospital room while wearing the device, but after therapy, is free to return home without posing any radioactive risk to family or other contacts. See page 2



Editorial Staff
Mary Donovan
Editor

Susan Gerhold
Associate Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

NIH News Branch
Building 31, Room 2B-10
B esda, Maryland 20205

Phone:
(301) 496-2535

Two new diagnostic tests have been recently developed to help scientists predict whether a child with Gaucher's disease, an inherited lipid storage disorder, will suffer nervous system involvement.

These tests will aid the physician in planning a course of treatment and provide precise genetic counseling, and at the same time, pinpoint which type of neurologic disorder, (acute or subacute) a patient may have. See page 5

A Consensus Development Panel convened recently at NIH, concluded that liver transplants offer a viable therapeutic alternative which may prolong life for some patients.

After considering two days of testimony from experts from all over the world and examining data from the four major centers where the procedure is performed, the Panel recommended that efforts be intensified to bring about an effective program for carrying out liver transplants. See page 10

The outstanding contributions to cancer research of four NIH grantees were recognized recently by awards from the General Motors Cancer Research Foundation.

Drs. Emil Frei III and Emil J. Freireich were honored for pioneering a combination chemotherapy program which virtually cured acute lymphocytic leukemia and established the principles that revolutionized cancer chemotherapy.

Dr. Bruce Ames was recognized for developing the world's most widely used screening test for mutagens and potential carcinogens and Dr. Raymond Erikson was honored as the first scientist to identify a chemical produced by a cancer gene. Their efforts have provided valuable information about the diagnosis, prevention and treatment of cancer. See page 6

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NCI and NIDR Develop Device to Treat Head and Neck Tumors

Jody Dove

A novel method of delivering radiation therapy to certain patients with malignant head and neck tumors is being used by researchers at the National Cancer Institute (NCI) working in conjunction with scientists and clinicians at the National Institute of Dental Research (NIDR).

The technique involves the use of an acrylic device, containing radioactive metallic seeds, that is made to fit externally over a patient's tumor. These appliances, called external-mold bite devices, are designed in collaboration with physicians and radiation physics scientists in the NCI Radiation Oncology Branch and are then constructed by Dr. William E. Wright and laboratory technician Albert D. McIntyre of the NIDR Dental Clinic.

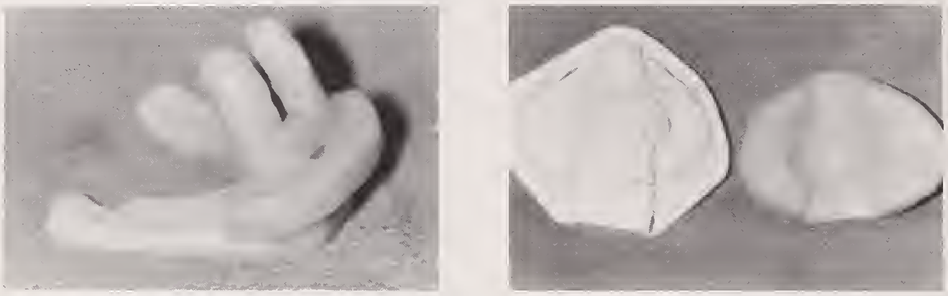
Each device consists of an intraoral mouthpiece on which the patient bites to provide proper positioning and stabilization, plus an extension that fits over the tumor to be treated (for example, on the lip, or tip of the nose). This external portion may be a single-unit extension of the mouthpiece or may be constructed of multiple units that interlock with the mouthpiece for stability.

Typically, cancer patients receive radiation therapy either through the use of machines that externally irradiate the tumor site or through the implantation of radioactive needles into the affected area.

External-mold bite devices offer an alternative method for treating those patients with head and neck tumors that are located close to the skin or mucous membrane surfaces of the mouth or nose. A major advantage of the device is that radiation can be delivered directly to the tumor mass with reduced exposure to normal tissue in adjacent sites. The technique is also adaptable and can be used in conjunction with other types of treatment, such as chemotherapy and surgery.

The design and fabrication of an external-mold bite device is a multifaceted process requiring close cooperation between the NIDR and NCI clinicians, scientists, and technicians.

Following a dental consultation, Dr. Wright and Mr. McIntyre meet with the NCI personnel to discuss the proposed device. Initially the device is formed in wax. First, the mouthpiece or bite portion of the device is constructed on stone models of the patient's teeth. Next, a wax form, which closely adapts over the tumor, is made. This may be done by making a stone cast of the facial anatomy or by free-sculpting the wax over the tumor site.



The external-mold bite device used in treating a tumor located on the tip of a patient's nose, consists of the mouthpiece on which the patient bites (left) as well as projections which fit into the patient's nose to deliver radiation intranasally. The photo on the right shows both stone and wax models of the tumor. The patient wears the intraoral and extranasal pieces at the same time while undergoing therapy.
NIH PHOTO 1891

The patient then models the wax device for NCI Dr. Allen Lichter, chief of the Radiation Therapy Section, Radiation Oncology Branch, and Robert Miller, a physicist in the Radiation Physics and Computer Automation Section. When it is determined that the trial wax device fits the patient satisfactorily, it is converted from wax into the final acrylic appliance by a standard dental laboratory procedure. The NCI group then estimates where the radioactive seeds should be placed within the external mold.

The appliance is returned to the Dental Clinic and Dr. Wright and Mr. McIntyre complete the next step by cutting grooves in the tissue side of the mold. Plastic tubes containing dummy (nonactivated) seeds are temporarily imbedded in these grooves. By using the dummy seeds, the scientists can accurately compute the most effective location and activity for the metallic seeds without being exposed to radioactive materials.

Using an "after loading" technique (meaning that the actual radioactive seeds are loaded into the external mold after precomputing the amount of radiation required to treat a particular patient), the NCI investigators prepare the device for active patient therapy.

The radioactive seeds selected for use in these particular molds are composed of Iridium-192. This radioactive material has a half-life of 72 days. Thus, it loses one-half its strength in this time as it undergoes radioactive decay. During the treatment regimen, the potency of the radioactive seeds is computed daily. As the seeds begin to lose some of their strength, the treatment time is lengthened accordingly to deliver a constant daily radiation dose.

Patients come to the Clinical Center on an outpatient basis to use the external-mold bite devices. The NIDR Dental Clinic staff provides an orientation program and prevention and control therapies for possible oral and dental side effects that may occur as a result of the radiation treatment. A typical radiation treatment regimen using this device may require that the patient wear the appliance 4 to 6 hours a day, 5 days a week, for 3 weeks. While the device is in use, the patient must stay in an isolated hospital room to avoid exposing others to radiation. The patient may read or watch television, and can communicate with researchers by telephone. When the daily therapy is completed, the patient is free to return home without posing any radioactive risk to family or other contacts. As a safety precaution, the radioactive device is stored in a lead box in the Radiation Oncology Clinic when not in use. When the total treatment regimen is completed, the device is sent to the Radiation Safety Branch, Division of Safety for proper disposal.

The external-mold bite devices play an important role, alone or in combination with other modes of oncologic therapy, in successfully treating certain patients with superficial tumors of the head and neck. ■

NICHD-Supported Scientists Design Test for Prenatal Diagnosis of PKU

Tineke Boddé

Using genetic engineering techniques, scientists have succeeded in developing a procedure to diagnose phenylketonuria (PKU) in unborn children as well as in healthy older siblings who may be carriers of the trait. The new test was developed by Dr. Savio L.C. Woo of the Baylor College of Medicine in Houston, through research funded by the National Institute of Child Health and Human Development (NICHD).

PKU is an inborn error of metabolism in which the affected person is unable to convert phenylalanine, a naturally-occurring amino acid essential for normal growth, into tyrosine. PKU can lead to severe mental retardation, behavioral problems, epilepsy, and other types of neurological impairment.

With an incidence of one per 14,000 live births, PKU is one of the most common metabolic disorders which, if untreated, invariably requires life-long institutional care. Most untreated children with PKU develop an IQ of no more than 20. PKU shows no symptoms at birth but if detected early through blood analysis, a special diet can prevent mental retardation.

PKU is found in most population groups but is rare in blacks and Ashkenazi Jews. Its heredity is recessive, that is, the disorder will not affect the offspring unless both parents possess the trait. However, any PKU parent can pass the gene on to the children and make them carriers.

With the help of recombinant DNA techniques, Dr. Woo and his research staff succeeded in cloning the gene for the human liver enzyme (phenylalanine hydroxylase) that—if absent or deficient—causes PKU. He then used this cloned gene in testing fetal cells obtained from the amniotic fluid of pregnant women. Using gene mapping (identifying the type and place of specific genes on a chromosome), he compared the fetal genes to those in parents and normal volunteers.

The major benefit of Dr. Woo's research is that, in families that already have one or more children with PKU, the new test enables the physician to accurately determine whether the fetus of a subsequent pregnancy is affected by the disorder (25 percent chance), and whether older unaffected siblings are carriers (50 percent chance each) or are free of the PKU trait (25 percent chance).

At present, PKU is diagnosed in the infant by blood analysis after birth. This test has become standard procedure in most developed countries in the past 20 years. A drop of blood is taken from the infant's heel between two and seven days after birth, after feedings (containing protein) have been initiated. Once diagnosed as having PKU, a newborn can be started immediately on a phenylalanine-restricted diet. NICHD-supported research has confirmed that children on the diet develop normally, both physically and mentally.

NICHD scientists believe the work of Dr. Woo and his colleagues, besides its predictive and diagnostic value, has greatly added to our understanding of the PKU gene and may eventually lead to an *in utero* treatment of PKU by gene substitution. ■

Fogarty International Center Organizes PAHO Day at NIH

Phyllis Eveleth

On June 17, the National Institutes of Health reached hands across the border [illegible] their neighbors in the South, the Pan [illegible]merican Health Organization (PAHO). The Director and seventeen administrators of PAHO were invited to exchange information with NIH administrators about programs in health research. The Fogarty International Center organized the meeting to expand collaborative relations between PAHO and NIH.

PAHO, which also serves as the Regional Office for the Americas of the World Health Organization, is concerned with public health, disease eradication, basic sanitation, manpower development, as well as biomedical research and communications.

At the recent meeting sponsored by the Fogarty International Center, presentations [illegible] made on various health topics of mutual interest to the NIH and the Pan American Health Organization. NIH PHOTO 1892

PAHO Director Dr. Carlyle Guerra de Macedo emphasized his organization's wish to promote research in Latin American countries and to improve technical excellence. He pointed out the need for contacts with research institutions, such as NIH and universities, for PAHO to take advantage of new research results and use them to solve health problems in Latin America. Although major problems traditionally have been infectious and parasitic diseases, now—as individual countries become more industrialized, more urbanized, and increase their number of elderly—the pattern is shifting to a higher incidence of chronic diseases, especially cancer and cardiovascular diseases.

Current common interests of NIH and PAHO were stressed in presentations on environmental health, cancer, cardiovascular disease, tropical diseases, laboratory animal health, and biomedical communications. Other areas of importance for further consideration are oral health, aging, arthritis, child health, blindness, and computer sciences.

During the talks, the value of NIH and PAHO collaboration in research was stressed and specific areas where collaboration could take place were highlighted. Among these are the International Program on Chemical Safety, supply of genetically-defined laboratory animals, compilation of special bibliographies on tropical diseases, and field testing of vaccines. Dr. Macedo pointed out that PAHO is uniquely suited to advise and assist the U.S. Public Health Service on health matters dealing with Latin America.

Dr. Carlyle Guerra de Macedo, Director of the Pan American Health Organization, stressed the importance of promoting medical research in Latin American countries. NIH PHOTO 1893

During their visit, the PAHO guests visited the National Institute of Allergy and Infectious Diseases' (NIAID) Laboratory of Parasitic Diseases and the insectary where research on malaria-carrying Anopheles mosquitos is carried out.

It is hoped that meetings such as "PAHO Day" will open the way for increased technical communications and collaboration between NIH and PAHO that will be mutually beneficial. ■

Study Indicates Vasectomy Does Not Increase Risk of Atherosclerosis

Maureen Gardner

In contrast to the results of earlier research in monkeys, a new study has found no relationship between vasectomy and atherosclerosis in men. Atherosclerosis—a form of hardening of the arteries—can lead to heart attack if it affects the coronary arteries, which supply the heart muscle with blood.

An estimated 10 million men in the U.S. have had vasectomies. Following vasectomy, men continue to produce sperm, which their bodies absorb. In more than half of all men who have had vasectomies, the body produces antibodies to the sperm. Several years ago, some research suggested that these antibodies, which circulate in the bloodstream, speed up the development of atherosclerosis in vasectomized monkeys.

More than 7,400 men took part in the new project, which was supported by the National Institute of Child Health and Human Development (NICHD). The patients were enrolled in the Milwaukee Cardiovascular Data Registry, a computer system that keeps track of people who have undergone angiography, x-rays of the blood vessels to measure atherosclerosis in their coronary arteries. Five percent, or 370 of the men, had had vasectomies.

The researchers compared the extent of disease in the men with and without vasectomies. "Our results provide no evidence for any association between atherosclerosis and vasectomy in men," according to Dr. Alfred Rimm, who headed the study at the Medical College of Wisconsin in Milwaukee. Dr. Rimm added that the study generally supports other research in humans that found no increased risk of heart attack in men with vasectomies.

"If vasectomy accelerated the blocking of coronary arteries, then the men with vasectomies would have more extensive coronary artery disease than the nonvasectomized men," according to Dr. Rimm. "The results show, however, that the vasectomized men do not have a higher degree of coronary artery blockage," he said. "In fact, the only trend that was noted was in the opposite direction. The vasectomized men actually had less coronary blockage than men their own age who were not vasectomized."

To see if the length of time following vasectomy affected the degree of atherosclerosis, the researchers analyzed separately 79 men who had undergone vasectomies at least 10 years before having an angiogram. They found no greater proportion of these men among the patients with serious cases of the disorder than among those with mild cases.

The researchers also looked at subgroups of men at the two extremes in extent of disease—those with the least coronary blockage and those who had severe blockage requiring coronary bypass surgery. Again, the men with vasectomies within both of these groups had no greater degree of blocked arteries than the men without vasectomies.

Although the study showed that vasectomy does not influence the severity of atherosclerosis, it did indict smoking, high levels of blood fats, and age. All of these increased the degree of coronary blockage in men with vasectomies, just as other research has indicated is the case for men in general. ■

Drug Responses Dependent on Differences in Gender

Marilyn Sargent

Sex hormones can significantly affect the way drugs are metabolized by the body, yet dosages and medication schedules for psychoactive and other drugs prescribed for both men and women are based on a greater understanding of male physiology, report National Institute of Mental Health (NIMH) scientists, Drs. Jean Hamilton and Barbara Parry.

"Many more men than women are included in initial clinical studies," they point out, "perhaps, in part, because of concerns about drug-testing during childbearing years."

However, it is well-documented that oral contraceptives and prescribed estrogens alter responses to a wide variety of commonly used drugs, including those prescribed for anxiety, depression, epilepsy, diabetes, Parkinson's disease and thyroid problems. Nevertheless, little thought has been given to how the hormones produced within the body, the endogenous hormones, interact with these medications. Even studies done with female subjects have generally overlooked the possible variances in drug response due to changes in hormonal levels during the menstrual cycle or after menopause, the intramural researchers contend.

More drugs are prescribed for women than for men and, proportionally, women have more adverse reactions to them. For example, women—particularly those past menopause—may be more vulnerable to tardive dyskinesia, a disorder associated with psychoactive drugs that is manifested by uncontrollable movements. Nevertheless, studies to elucidate drug action—even with animals—are limited for the most part to male subjects precisely to avoid dealing with the effects of the female hormonal cycle, "often seen as a confounding variable in laboratory experiments," say the researchers.

"However new basic science data, often in projects initiated by women researchers, have documented profound effects of estrogen on brain dopamine, serotonin, and opioid physiology.

"Perhaps the preponderance of women with adverse drug reactions does not merely reflect sex-related differences in the reporting of symptoms, but also reveals our relative neglect of women's physiology," they note in an article to be published in the September issue of the *Journal of the American Medical Women's Association*.

The article, described by Hamilton as an introduction to "gynecological pharmacology," summarizes research on how prescribed estrogens and birth control pills affect the metabolism, responsivity, and toxicity of major drug groups.

The findings give "evidence for sex-related differences, as well as menstrual and menopausal variations, in a variety of neurochemical systems," and underscore the need for studies on the effects of endogenous hormones, according to the scientists.

"Just as the emerging discipline of chronopharmacology has begun to look at drug effects and optimal dosages according to the time of day in male rats, perhaps we need to take a closer look at effects according to the time of month," they point out.

To illustrate one fruitful research area, the investigators cite neurochemical clues to possible answers about the preponderance of depression in women. In fact, Hamilton and Parry both see their work on the menstrual cycle as pertinent to the question of women and certain subtypes of depression. The investigators, who presented preliminary findings at the May 1983 American Psychiatric Association "Symposium on Premenstrual Changes," have been looking at a variety of neuroendocrine measures that may have relation to such premenstrual symptoms as increased stress in some women.

The need to look at the links between hormonal alterations during the menstrual cycle and major depression is borne out by evidence that women with premenstrual syndrome (PMS) more often experience atypical depression—increased rather than diminished appetite, sleep, and sexuality—than do depressed women who do not suffer from PMS. Also, atypical depression more often responds to a different class of drugs—the MAO inhibitors—than to the tricyclics, which are effective for most typical depressive disorders. Altered hormonal levels in these women may account for the differences in symptoms and suitable medication.

The scientists conclude that: "A systematic examination of sex-related differences in drug responsivity may help to develop a medical science that better pertains to all people, including the more than 50 percent who are female." ■

New Tests for Gaucher's Disease Predict Nervous System Involvement

Diane Striar

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) scientists have developed two new diagnostic tests that can predict whether a child with Gaucher's disease will eventually show nervous system involvement. Gaucher's is an inherited lipid storage disorder and is characterized by an abnormal buildup in tissues of glucocerebroside—a complex fat or lipid. Glucocerebroside accumulates because of a genetically determined defect in an enzyme called glucocerebrosidase, that normally breaks down the lipid.

The tests will help scientists plan a course of treatment and provide precise genetic counseling for Gaucher's patients, says Dr. Roscoe O. Brady, chief of the NINCDS Developmental and Metabolic Neurology Branch where the research was conducted.

Both tests indicate whether a patient suffers from the type of Gaucher's disease that does not affect the nervous system, or instead has one of the two neurologic types.

The second test further discriminates between the two neurologic categories of the disease.

Drs. Edward I. Ginns and John A. Barranger developed the tests after identifying genetically distinct varieties of the defective enzyme that causes the disease. NINCDS scientists are investigating this disorder in the hope that it will be a prototype for the study of all lipid storage disorders.

There are three types of Gaucher's disease:

Type 1 (non-neurologic): involves the liver, spleen, lung, and bones;

Type 2 (acute neurologic): causes severe mental and physical retardation and leads to death before age two;

Type 3 (subacute neurologic): causes seizures and eye movement abnormalities in children, and usually involves all of the symptoms of type 1.

The standard method of diagnosis does not identify which type of Gaucher's disease a patient has, or—in the case of prenatal detection—which kind a fetus will develop.

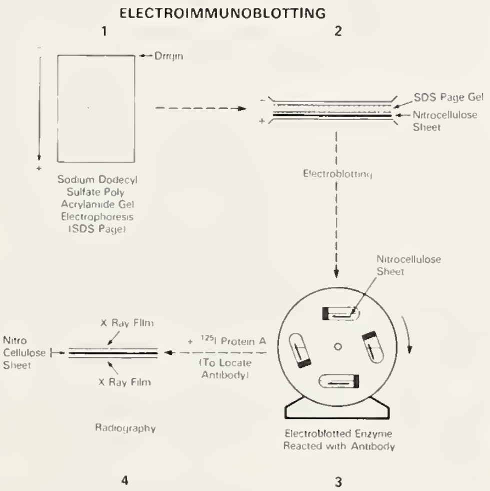
"It is obviously very important to be able to distinguish among these patients to develop rational therapeutic strategies for those who have the disease," says Dr. Brady.

There is as yet no treatment for patients who have the neurologic types of Gaucher's disease, according to Dr. Brady. Patients without neurologic involvement may be helped by replacement of the defective enzyme in much the same way that diabetic patients are treated with insulin.

Drs. Ginns and Barranger have used the new tests to diagnose several dozen Gaucher's disease patients. The scientists are now studying the usefulness of the tests in prenatal diagnosis.

"When these prenatal versions are ready for clinical use, they will have a tremendous impact on genetic counseling," Dr. Brady predicts.

The new tests rely on a laboratory technique called electroimmunoblotting. Drs. Ginns and Barranger use electrophoresis to extract enzymes from Gaucher's patients' cells and from cells of normal persons, and transfer the enzymes from separating gels onto a nitrocellulose paper. A specific enzyme antibody and a radioactive protein are then added to the enzyme mixture. When x-ray film is placed on top of the paper and exposed, the radioactive compound acts as a probe, revealing glucocerebrosidase as a collection of bands. The bands of both Gaucher's patients and normal individuals can then be compared on the same nitrocellulose paper.



NIH PHOTO 1894

According to Dr. Ginns, normal glucocerebrosidase is seen as a series of three bands—each one a different size.

"Each band corresponds to a stage in the normal maturation process of the enzyme," he says. "The enzyme is largest when it is first synthesized in the cell. Then it is broken down to two successively smaller molecules. The smallest one appears to be the biologically active form within the cell. This is the form of the enzyme that actually breaks down the lipid."

The NINCDS investigators found the three enzyme bands in both normal cells and cells from type 1 Gaucher's patients, those without nervous system involvement.

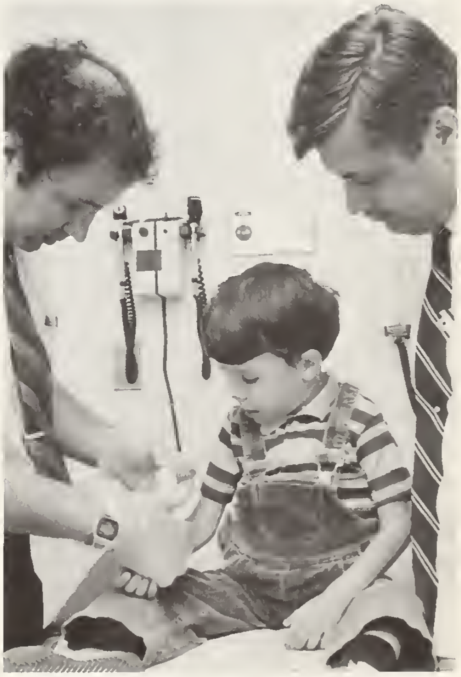
But in cells extracted from patients with types 2 and 3, the smallest band—the active form—was not visible, indicating a lack of the mature enzyme.

This discovery enabled the scientists to predict whether a patient will have the non-neurologic or neurologic type of Gaucher's disease.

The second test uses a monoclonal antibody developed by the NINCDS research team in collaboration with scientists in the Netherlands to further distinguish between the two neurological types of the disease. The monoclonal antibody reacts with the largest enzyme band in tissue extracts from type 3 patients, but does not react with this band in tissue from type 2 patients.

Additional studies are now under way to find out why the antibody reacts to the type 3 Gaucher's enzyme but does not react to the enzyme in type 2 patients.

The NINCDS scientists collaborated with Dr. Joseph M. Tager and coworkers at the University of Amsterdam and Dr. Hans Galjaard and his colleagues at Erasmus University, the Netherlands. The most recent report of this research can be found in *Clinica Chemica Acta*, July 15, 1983. ■



Drs. Edward I. Ginns and John A. Barranger finish skin biopsy procedure on a small Gaucher's patient. The skin biopsy is taken first and then the scientists can begin to identify the different forms of the defective Gaucher's enzyme, by the two new tests that were recently developed. NIH PHOTO 1895

NIH Grantees Honored for their Cancer Research

Sandra D. Levine

Four scientists were honored recently with awards from the General Motors Cancer Research Foundation for their outstanding contributions to this field of medicine. The work of all the recipients was supported by NIH grants, and indeed three of the four began their illustrious careers at NIH.

On June 15, the award winners presented lectures at the Clinical Center about their research. Introducing the winners, Awards Assembly Chairman Dr. Jonathan Rhoads likened these prestigious awards to the "Nobel Prizes" of cancer research.

The Charles F. Kettering Prize was awarded jointly to Drs. Emil Frei III and Emil J. Freireich for their outstanding accomplishments in the diagnosis and treatment of cancer.

They first began working together at the National Cancer Institute almost 30 years ago, and their association led to the development of an intermittent combination chemotherapy program for children with acute lymphocytic leukemia. This program revolutionized cancer treatment and provided the cornerstone for modern cancer chemotherapy.

Their 17-year collaboration led to the development of "the first treatment for leukemia that truly cured patients," according to the award citation. And in the process, they established most of the principles of chemotherapy trials for all kinds of cancers.

In 1955, when Drs. Frei and Freireich joined the National Cancer Institute as senior investigators, acute lymphocytic leukemia, usually found in children, was always fatal within a very short time. Drugs that could kill the leukemic cells acted too slowly—methotrexate, for example, took about six weeks to take effect. During this time patients died of infections, hemorrhages, and metastases of the leukemic cells to the central nervous system. Less than one percent of the patients were living long enough for the drugs to work.

Drs. Frei and Freireich, therefore, first tried to overcome these barriers to treatment by investigating ways to keep the patients alive until the drugs could take effect. In the late 1950's, they showed that such measures as transfusions of white blood cells, and preventive use of antibiotics and germ-free isolation rooms, reduced the number of deaths from infection.

Blood transfusions were insufficient to control hemorrhaging—another life-threatening complication for leukemia patients, since they could not produce functioning platelets to bring about clotting. Drs. Frei and Freireich showed that bleeding could be prevented by transfusing only platelets. This method, plus giving platelets from a single donor to avoid immune complications from repeated transfusions of foreign blood, drastically lowered the number of deaths from bleeding. Dr. Freireich also devised the first continuous flow blood cell separator.

Thanks to the work of Drs. Frei and Freireich, by the early 1960's children with leukemia were surviving for a few months—time that was crucial for the drugs to act.

These researchers now turned their attention to making the available drugs more effective, and it was here that they revolutionized cancer therapy.

In 1961, they showed for the first time that two drugs administered simultaneously worked better than when given sequentially. They also gave their patients larger doses, which proved more effective, and for shorter periods of time, allowing normal cells to recover between treatments. They also tried drugs, like Vincristine, that had been considered too toxic, but is now in widespread use today, thanks to their efforts.

In 1962, Drs. Frei and Freireich conducted a drug trial that became a landmark in cancer treatment. Of the five drugs capable at that time of killing malignant cells, they used four in combination. The drugs were: Vincristine, Amethopterin, Mercaptopurine, and Prednisone, giving the study its name, the VAMP program. Given to 16 patients, 14 had complete responses.

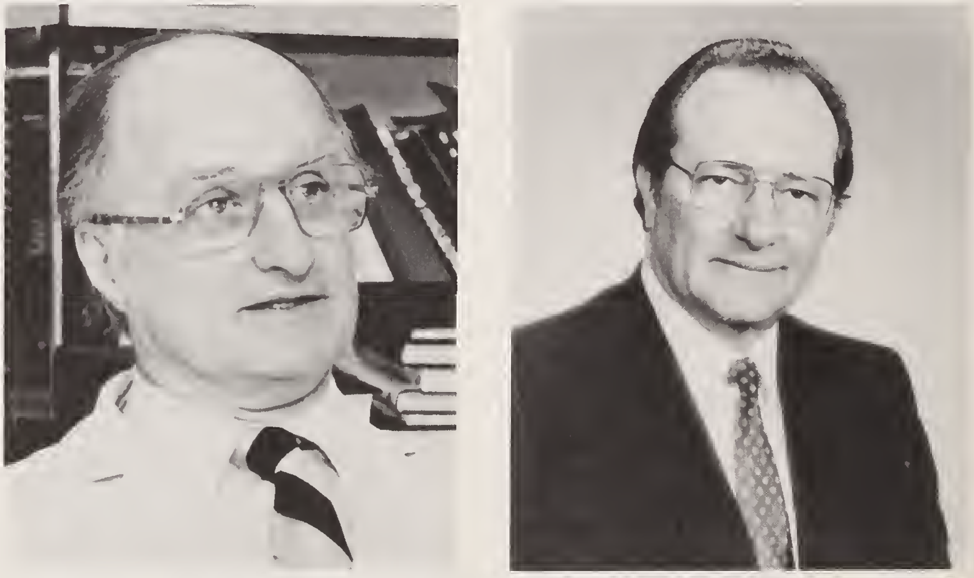
This was a dramatic improvement th[illegible] blazed the trail for future cancer therapies. It was the first time that a drug trial had incorporated four drugs in one treatment. It showed that side effects were not increased, and VAMP was the first trial to include intensive drug therapy during remission, known as adjuvant therapy. It was also the first time that the length of remissions was used to measure the effectiveness of treatment.

Th VAMP program, which was a prospectively designed curative-intent protocol, showed that all a patient's malignant cells must be destroyed, because if even a few remained, they could later spread. Therefore, maintenance therapy was added to future protocols.

A study of the survival rate for patients with acute myelogenous leukemia at the M.D. Anderson Hospital and Tumor Institute in Houston showed that in 1965, only nine percent had complete remissions (i.e. elimination of the leukemic cells from the primary site of the disease—the bone marrow—with no other metastases) using the best chemotherapy efforts available. By 1976, using Drs. Frei and Freireich's principles of combination chemotherapy, the remission rate was 66 percent.

Drs. Frei and Freireich also conduc[illegible] studies to find ways to circumvent [illegible] barrier that prevents drugs from entering the brain, because leukemic cells can migrate to areas, such as the central nervous system, that are protected from drugs.

As well as establishing almost all the



Dr. Emil Frei, III, (left) and Dr. Emil J. Freireich (right) were the recipients of the Charles F. Kettering Prize for their work in curing leukemia and their profound effect on the principles of cancer chemotherapy.

NIH PHOTO 1896

principles for curing leukemia (a remission lasting at least four years indicates a 90-95 percent probability of cure), Drs. Frei and Freireich also determined many of the criteria used in anti-cancer drug trials today. The guidelines they established have been used in developing treatment for many types of cancer, such as Hodgkin's disease, non-Hodgkin's lymphoma, metastatic germ cell tumors, osteogenic sarcoma, and in the growing advances against the more common malignancies of the breast, lung, and colon. For example, the use of combination chemotherapy for squamous cell carcinoma of the head and neck has led to a response rate of about 90 percent.

Drs. Frei (extreme left) and Freireich (extreme right) recently met with one of the thousands of children who are alive today because of their combination chemotherapy for leukemia. NIH PHOTO 1897

Drs. Frei and Freireich have performed many remarkable achievements, but perhaps the most profound is that more than ten thousand children in the U.S., who thirty years ago would have died of leukemia, are alive today because of their efforts.

Dr. Bruce N. Ames received the Charles S. Mott Prize for cancer prevention for his development of the world's most widely used screening test to determine whether a chemical is likely to be carcinogenic. Dr. Ames, who began his career at NIH, has had a very important effect on reducing potentially hazardous chemicals in the environment.

Using genetically developed bacteria, the Ames test measures whether a chemical can cause damage to genes. This process of mutation is considered to be closely associated with carcinogenesis. The test is currently used in over three thousand laboratories worldwide as a preliminary warning system for detecting mutagens and possible carcinogens.

In the 12 years since its inception, the Ames test has been used on over five thousand chemicals, such as the flame retardant tris, and on other potentially dangerous substances which have been eliminated from products before ever reaching consumers.

Dr. Bruce Ames was the winner of the Charles S. Mott Prize for his development of a screening test for mutagens and potential carcinogens. NIH PHOTO 1898

As well as developing the screening test, Dr. Ames was one of the first scientists in the early 1970's to show the correlation between mutagenicity and carcinogenicity. He also helped to clarify how DNA mutations occur, and recently began identifying naturally occurring anti-cancer substances. He and his colleagues showed that about 85 percent of a list of carcinogens they tested produced mutations in bacteria. Since relatively few chemicals are mutagenic, the test can usually discriminate between those that are safe and those potentially carcinogenic.

The test uses four strains of Salmonella that are especially sensitive to different kinds of chemicals. It has been further refined to make it more closely simulate what happens in the body as metabolic processes act on chemicals. The test is even able to determine that certain mutagens are excreted in the urine of cigarette smokers that are not found in the urine of non-smokers.

Dr. Ames has recently been investigating oxidation reactions in the body and their effects on DNA damage and on aging.

Dr. Ames' studies have had a major impact on understanding the processes of mutagenesis and carcinogenesis and the relationship between them. His research has paved the way towards protection from exposure to many potentially dangerous substances, and eventual enjoyment of a healthier environment.

The Alfred P. Sloan, Jr., Prize was awarded to Dr. Raymond L. Erikson, the first scientist to identify a chemical produced by a cancer gene—a major step towards understanding how the cancer process begins.

Dr. Erikson's study, reported in 1977, has already provided the impetus for a new field of study of the biochemical changes that result in normal cells becoming cancerous. Several other chemicals made by cancer genes have since been discovered, supporting the belief that a few biochemical changes are responsible for the development of most types of cancer.

All cancers are characterized by uncontrolled growth and disorganization of the cell, but how these alterations are triggered has eluded scientists. In 1977, however, Dr. Erikson identified a virus-coded enzyme in the cells of animals infected with Rous sarcoma virus—for the first time defining what a cancer gene produces inside a normal cell.

Dr. Raymond Erikson received the Alfred P. Sloan Prize as the first scientist to identify a chemical made by a cancer gene.

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After discovering that the Rous sarcoma virus could induce cancer by producing a single new protein, Dr. Erikson then went on to identify that the chemical was an enzyme of the protein kinase type. The function of protein kinases in the body is to add a phosphorus atom to simple amino acids. This process of "phosphorylation" can profoundly affect body processes by completely changing a chemical and its cellular function. The protein kinases made by cancer genes were found for the first time to add phosphorus atoms to tyrosine, an amino acid not previously believed to be involved in phosphorylation.

Dr. Erikson's work indicates that the protein kinase enzyme can stimulate changes in a normal cell's structure and rate of growth, causing it to become a cancer cell. His research has provided invaluable information about the malignant process and has had a profound effect on cellular studies of cancer. ■

Developments in Vision Research Presented at Science Writers' Seminar

Bobbi Bennett

Dr. Goldberg (standing) monitors and analyzes eye movements using a computer.

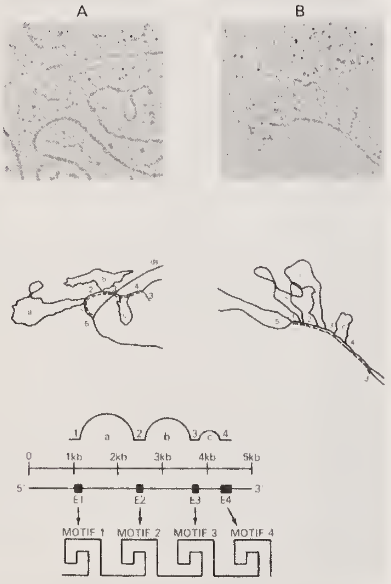
NIH PHOTO 1901

Advances in our understanding of the visual process from the level of the gene to that of the brain were highlighted at a recent NIH Science Writers' Seminar.

Dr. Joram Piatigorsky, chief, Laboratory of Molecular and Developmental Biology, National Eye Institute (NEI), served as moderator and also discussed the spatial and developmental distribution of the family of structural proteins of the lens known as crystallins. The dense packing of these proteins is responsible for the lens' transparency.

Research has shown remarkably similar structure between two immunologically distinct classes of these proteins—the β and γ crystallins which are found in all vertebrates. In collaboration with English researchers, Dr. Piatigorsky and his colleagues recently found that each of the four exons of a β-crystallin mouse gene encodes one of the four structural motifs of the protein, linking the gene structure with protein structure in this major mouse lens protein. Dr. Piatigorsky and Charles King have shown that some exons in the crystallin genes may be used alternatively, providing a source of variation for protein structure among the crystallins.

Studies by NEI scientists Deborah Carper and Drs. Piatigorsky, Toshimichi Shinohara, and Jin Kinoshita have shown that Philly mice, a strain that develops a hereditary cataract approximately four weeks after birth, have a deficiency of functional messenger RNA for a major B-crystallin. This defect precedes the development of the cataract. Progeny of normal and Philly mice have intermediate levels of this protein and a delayed onset of the cataract. If this deficiency causes the membrane damage leading to the cataract, it could provide an experimental model for attempting to repair ocular disease by genetic engineering.



Electron micrograph of a mouse β-crystallin gene hybridized to its mRNA (A) or to its complementary DNA (B) showing the looping out of the noncoding introns (a,b,c). The gene has four exons. Each exon codes one structural motif of the β-crystallin protein.

NIH PHOTO 1900

A survey of research on how the retina's rods and cones convert photons of visible light into neural signals that the brain can use was presented by Dr. William Hagins, chief, Membrane Biophysics Section, Laboratory of Chemical Physics, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK).

He and Dr. John George have shown that cyclic nucleotides, in collaboration with the rest of the rod's cellular machinery, cause calcium ions to be accumulated within its photosensitive disks in the dark and released in the light.

Their finding supports a current theory of light activation in which light causes photochemical reactions to occur in rhodopsin—the light sensitive protein in the rods—which in turn causes a series of biochemical steps, one of which involves the splitting of cyclic nucleotides. This then changes the level of calcium ions in the cytoplasm, shutting down the sodium channels, and eventually causing a change in the conductance of the plasma membrane which is transmitted along the cell to the neuron.

Dr. Gerald Chader, chief, Laboratory of Vision Research, NEI, discussed his work on the role of cyclic GMP in normal photoreception and in animal models of retinitis pigmentosa (RP), a hereditary disease which causes degeneration of the photoreceptor cells of the retina, resulting in progressively impaired vision, and, ultimately, blindness.

He has identified the basic biochemical lesion in some animal forms of RP to be an abnormally low level of the enzyme phosphodiesterase (PDE) which leads to destructively high levels of the intracellular messenger cyclic GMP and retinal degeneration. In one animal model, Dr. Chader has found that an activator of PDE, calmodulin, can raise the levels of this enzyme during the critical early developmental period. If the same biochemical lesion is found to exist in human forms of RP, use of such an activator and new techniques such as gene therapy could provide the first means for treating or preventing this disease.

Dr. Michael Goldberg, chief, Section of Neuro-Ophthalmological Mechanisms, Laboratory of Sensorimotor Research, NEI, discussed his work on the mechanisms by which the brain translates neural impulses generated in the retina into visual behavior such as eye movement and visual attention.

By studying the activity of single neurons in the brains of monkeys as they responded to spots of light in various fields, Drs. Goldberg, Bushnell and Robinson have been able to distinguish different patterns of activity in the posterior parietal cortex and the frontal eye fields, the parts of the brain thought to be related to the control of eye movement. Activity in the frontal eye fields was found to be specifically related to the process of making a visually guided eye movement. However, activity in the posterior parietal cortex was related to the process of general visual attention and not limited to any specific motor process.

Understanding of the physiology of attention in monkeys will enable scientists to study these types of phenomena more carefully in humans with the hope of developing rehabilitative strategies for patients with neuro-ophthalmological disorders such as stroke. ■

Studies Find No Link Between Certain Cancers and the Use of Oral Contraceptives

Maureen Gardner

NIH PHOTO 1902

More than 40 million American women have used oral contraceptives since 1960, when "the pill" was introduced in the U.S. During these years of widespread use of the pill, many women feared that it might increase their risk of cancer. Because cancer takes a long time to develop, early studies could not address this concern.

Now, more than two decades after women in the U.S. started taking the pill, a new study of more than 5,000 women has brought reassuring news. Early results from the Cancer and Steroid Hormone Study show that the pill does not increase a woman's chances of developing breast cancer. The study also found that women who have taken the pill are actually half as likely as other women to develop cancer of the ovary and endometrium (lining of the uterus).

The Cancer and Steroid Hormone Study is an ongoing project involving more than 1,000 women with cancer and a comparison group of more than 4,000 healthy women. It is the first study designed to look at the long-term risk of cancer, both in women who started taking the pill many years ago (up to 15 years or more) and in those took it for a long time (11 years or more). The project is supported by NICHD and the National Cancer Institute (NCI), and performed by researchers at the Centers for Disease Control (CDC).

The study focuses on cancer of the reproductive system—the breast, ovary, and endometrium—three of the leading types of cancer in women. Some of the risk factors for these cancers involve a woman's hormone status, such as her age at the start of puberty or when she had her first child. Doctors were concerned, therefore, about how these cancers might be affected by the hormones contained in oral contraceptives.

The largest portion of the study involved breast cancer, the leading cause of death by cancer for women in the U.S. About 1 in 14 women develop the disease. Researchers found that women who have taken the pill are no more likely to develop breast cancer than are women who have never taken it.

According to the study, even women who have taken the pill for a long time (11 years or more) do not appear to have an increased risk of breast cancer. Unlike some earlier research findings, this study showed that the pill does not add to the chances of breast cancer in women who already have a greater than average risk of the disease, such as those with benign breast disease or a family history of breast cancer.

The researchers also examined endometrial cancer, the third most common cancer in U.S. women. They found that oral contraceptives containing both an estrogen and progestogen—"combination pills"—protect women from the disease. Women who have taken combination pills for at least one year have half the risk of women who have never taken the pill. In addition, the study showed that the pill protects women from ovarian cancer, the fourth leading cause of cancer deaths in U.S. women. The researchers estimate that the pill prevents about 2,000 cases of endometrial cancer and about 1,700 cases of ovarian cancer each year.

Birth control pills still hold risks for some women. For example, women over 35, smokers, and women with high blood pressure (or other risk factors for heart disease) have higher chances of developing serious complications of the pill, such as heart attack or stroke. But for young, healthy, nonsmoking women, these risks are slim. And for all women who have used oral contraceptives, the results of the new study on cancer are encouraging. ■

NIH Consensus Conference Sees Liver Transplants as Promising

Irving Shapiro

An NIH Consensus Development Panel, composed of liver specialists, transplant surgeons, internists, pediatricians, statisticians, an ethicist and a public representative, has stated that liver transplantation is a useful therapy that deserves broader application for end-stage or life-threatening liver disease. However, in order to attain its full therapeutic potential, the procedure "must be the object of comprehensive, coordinated, and ongoing evaluation in the years ahead." The Panel indicated that this can best be achieved by expansion of the technology to a limited number of transplant centers where the operation can be performed under optimal conditions.

Since Dr. Thomas Starzl performed the first human liver transplant in 1963, over 540 such operations have been carried out in four medical centers—in Pittsburgh, The Netherlands, England and West Germany. Additional operations have been performed in other parts of the world and in several other American medical centers. Although extremely demanding, the procedure has been shown to be technically feasible, and interpretable results have been reported from all four primary transplant centers. These clearly demonstrate that liver transplantation offers an alternative therapeutic approach which may prolong life in some patients suffering from severe liver disease that has progressed beyond the reach of currently available treatment and consequently carries a predictably poor prognosis. However, substantial questions remain regarding selection of patients who may benefit from liver transplantation; the stage of their liver disease at which transplantation should be performed; survival and clinical condition of patients beyond the initial year after transplantation; and overall long-range benefits and risks of transplantation in the management of specific liver diseases.

To resolve some of these issues, on June 20-23, 1983, NIH convened a Consensus Development Conference on Liver Transplantation.

The Conference was sponsored by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) and the NIH Office of Medical Applications of Research (OMAR). Expert presentations of the available data were made by liver specialists, transplant surgeons, immunologists, biostatisticians and epidemiologists from many parts of the world. Key questions addressed were:

—Are there groups of patients for whom transplantation of the liver should be considered appropriate therapy?

—What is the outcome (current survival rates, complications) in different groups?

—In a potential candidate for transplantation, what are the principles guiding selection of the appropriate time for surgery?

—What are the skills, resources, and institutional support needed for liver transplantation?

—What are the directions for future research?

The survival rate for liver transplants appears to have increased significantly in the past several years, probably due to a number of factors including the use of the immunosuppressive drug Cyclosporin A, which lessens the body's tendency to reject transplanted tissue.

The Panel determined that appropriate candidates for transplantation include children and adults suffering from irreversible liver injury who have exhausted other medical and surgical treatments, and are approaching the terminal phase of their illness. According to the Panel, experience so far has shown that life can be prolonged by transplants for patients with the following serious liver conditions:

—*Extrahepatic biliary atresia* which is the most common cause of bile duct obstruction in the young infant, affecting one in ten thousand neonates. It is usually fatal within 18 months if untreated. Patients who fail to respond to hepatoportoenterostomy (Kasai procedure) often benefit from liver transplantation. Recent data suggest that as many as two-thirds of these patients survive for one year or more after transplantation.

—*Chronic active hepatitis* is caused by viral infections or drug reactions, but many cases remain unexplained. Although some patients with progressive liver failure are candidates for transplantation, exceptions include drug-induced chronic active hepatitis, which usually responds to removal of the chemical agent, and hepatitis B-induced disease in which viremia persists. In the latter instance, rapid reappearance of infection with progressive liver failure has been reported following transplantation.

—*Primary biliary cirrhosis,* a slowly progressive cholestatic liver disease. Results of transplantation appear favorable for patients with end-stage liver injury. The procedure may improve the quality of life.

—*Inborn errors of metabolism* may cause end-stage liver damage or irreversible extrahepatic complications. Transplantation may be appropriate for such patients.

—*Hepatic vein thrombosis* (Budd-Chiari syndrome) often results in progressive liver failure, ascites (accumulation of fluid in the abdomen), and death. Patients who have not responded to anticoagulation or appropriate surgery for portal decompression may be candidates for transplantation.

—*Sclerosing cholangitis,* a chronic non-suppurative inflammatory process of the bile ducts, may cause liver failure. Less favorable results following transplantation in this group may be due to prior multiple surgical procedures, a diseased extrahepatic bile duct, the presence of biliary infection, or other factors, but no other beneficial therapy is available.

—*Primary hepatic malignancy* confined to the liver but not amenable to resection may be an indication for transplantation. Results to date indicate a strong likelihood of recurrence of the malignancy. Nonetheless, the procedure may achieve significant palliation.

—*Alcohol-related liver cirrhosis and alcoholic hepatitis* are the most common forms of fatal liver disease in America. Patients who are judged likely to abstain from alcohol and who have established clinical indicators of fatal outcome may be candidates for transplantation. Only a small proportion of alcoholic patients with liver disease would be expected to meet these rigorous criteria.

Although fulminant hepatic failure with massive hepatocellular necrosis induced by hepatitis viruses, hepatotoxins, or certain drugs may warrant liver transplantation, rapid progression of the disease and multi-organ system failure frequently preclude this option.

The Panel considered the survival and complication rates of patients who have undergone liver transplantation. The interpretation of the exiting data on survival from the four centers is extremely difficult because no control data are given for comparison, surgical techniques and drug therapies varied over time, and patient selection criteria and management differed across centers.

Although data are therefore insufficient to thoroughly assess the procedure, some of the trends the Panel noted include:

- Patients currently being accepted for transplantation have a high probability of imminent death and a low quality of life in the absence of transplantation.
- Patients undergoing transplantation have an operative mortality (within

NIH PHOTO 1903

one month) of 20 to 40 percent.

- One-year survival among transplant recipients since 1980 is favorable when compared with their expected course in the absence of transplantation.
- Since 1980, one-year survival appears improved over the earlier transplant experience.
- Individual patients have survived for many years with good quality of life after transplantation.

Severe complications of transplantation frequently occur. Massive hemorrhage is the most serious problem during and after the operation. Other postoperative complications include renal dysfunction, rejection, biliary tract complications, graft vascular obstruction, and infection. With accumulating medical and surgical expertise and improving technology, these complications can be expected to diminish.

The Panel could not specify the optimal time for transplant surgery. However, they said that transplantation should be reserved for patients in any of the following phases: when death is imminent; when irreversible damage to the central nervous system is inevitable; or when quality of life has deteriorated to unacceptable levels.

The Panel stated that the requirements for conducting a liver transplantation program are so formidable that any institution embarking on this program must make a major commitment to its support. "Liver transplant patients are seriously ill before surgery" they said. "The transplant effort is prodigious, and the postoperative intensive care interval, averaging two weeks, is punctuated by complications and frequent need for reoperation." In this context, a host of experts are needed to complement a qualified transplantation team. The transplantation surgeon must be trained specifically for liver grafting and must assemble and train a team to function whenever a donor organ is available. Institutional commitment to the program mandates that operating room, recovery room, laboratory, and blood bank support exist at all times. Of course participation in a donor procurement program and network is essential, and an interdisciplinary deliberative body should exist to determine on an equitable basis the suitability of candidates for transplantation. Surgeon General Dr. C. Everett Koop reported to the Panel that a task force is being established to look into more effective mechanisms for organ procurement.

Regarding future research, one of the Panel recommendations included the establishment of a registry or clearinghouse for the collection and evaluation of all available data on liver transplantation. Such a center would develop unified criteria for selection of patients for transplantation and for reporting and evaluating all data related to the outcome of the operation and the patient's postoperative and long-term condition.

The Panel also said that high priority should be given to studies related to several aspects of the procedure itself, such as improved preservation of the donor liver before transplantation and improved control of organ rejection. They asked that research into the causes, pathogenesis and natural course of chronic liver disease "be fostered and supported by all available means." Liver disease is the seventh leading cause of death in the U.S.

Copies of the Panel's statement are available from the NIH Office of Medical Applications of Research, Building 1, Room 216, phone (301) 496-1143, or the NIADDK Office of Health Research Reports, Building 31, Rm. 9A04, phone (301) 496-3583. ■

Caring Behavior is Manifested by Even Very Young Children

Judy Folkenberg

Children as young as 18 months of age show feelings of guilt, sympathy, and altruism, often reaching out to comfort a sad parent or a crying playmate, according to Dr. Carolyn Zahn-Waxler of the National Institute of Mental Health (NIMH).

Focusing on the caring characteristics of very young children, Zahn-Waxler and her colleagues, Dr. Marian Radke-Yarrow and Dr. Robert King, have concentrated on a side of children that most researchers have ignored. Their findings could significantly alter current concepts of child development which mainly see young children as self-centered little beings.

"Often our theories bias us against seeing the caring characteristics in children," says Zahn-Waxler. "Caring behavior often is quietly and subtly conveyed. It does not carry with it the 'drama' of a child's temper tantrum or acute state of woe.

"If we properly understand the beginnings of guilt, empathy, and altruism, we might reach a better understanding of some of the emotional disorders of childhood and adulthood," she notes.

"For instance, the antisocial personality is characterized by a lack of guilt or lack of feelings of responsibility. At the other extreme, the crippling effect of too much guilt has been linked with the development of anxiety disorders and depression.

"Likewise, balanced amounts of empathy and caregiving are an integral part of an individual's well-being. Too much empathy or hypersensitivity towards the distresses of others may hamper adaptive self-growth. And too little characterizes such psychological disorders as narcissism, egocentrism, and difficulties in establishing caring relationships with others."

Over a period of nine months, the NIMH researchers studied 24 male and female infants between the ages of 10 and 20 months. Five years later, they studied the toddlers for a three-month period. The mothers, used as trained observers, recorded approximately 2,000 incidents for the researchers for later analysis. To guard against bias, a second study used videotapes of children's reactions to others' distress to verify the mothers' observations.

The researchers discovered that between 12 and 15 months of age, when altruism is just beginning, the children made simple, positive physical contacts with the "victims," either by touching, patting, or giving them objects. Between 18 months and 2 years, children were seen to protect, comfort, give simple advice, and mediate fights.

During the second year of life, children also showed signs of developing a conscience and subsequent guilt feelings. When children caused someone distress, they often were apologetic. A few children would apologize repeatedly—even for injuries they did not inflict.

Rearing practices also influenced the degree of altruism and guilt in young children.

"Empathic mothers—very responsive mothers who help children promptly in times of distress—were significantly, more likely to have children who were highly altruistic," says Zahn-Waxler. However, the scientists discovered that empathic mothers also were more likely to use strong discipline when their children caused distress.

Strong discipline included: high expectations of absolute adherence to rules about never hurting others (e.g., "you mustn't ever bite"), moralizing ("it's not nice to do that"), or strong verbal commands against hurting.

The researchers speculate that a combination of nurturance and strong discipline creates heightened sensitivity in the child. They also believe that parents can be taught specific techniques to encourage caring behavior in children, which can sensitize the parents "to the early emerging humanity of their children." ■

MEDICAL CAPSULES

Sandra D. Levine

- The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has established a new Hearing Research Study Section.

The Section will review grants and training applications in many areas of prevention, diagnosis and treatment of auditory disorders. These will include studies of the basic and clinical aspects of middle ear diseases (e.g. otitis media), of inner ear diseases (e.g. tinnitus), and of auditory and neurosensory tumors.

- The National Library of Medicine (NLM) will add two new databases to its network this summer.

The Director of Information Resources Online (DIRLINE) will provide descriptions of sources of information available to meet needs not answered by bibliographic citations. DIRLINE lists and describes 13,000 organizations that provide specialized information on a wide variety of subjects.

CANCEREXPRESS, the other database, will provide technical information for cancer researchers and clinicians who want to retrieve information from selected journals. It will contain about 10,000 records describing articles in over four hundred high-quality publications for the most recent four-month period. It will provide bibliographic records identifying articles covering all aspects of the treatment etiology and biology of cancer, and studies of mutagenic and carcinogenic agents.

- It appears that kidney transplant recipients, although initially at high risk of graft loss and death, have a higher survival rate than patients receiving dialysis, once they stabilize in the months following transplantation.

This finding is the result of a study analyzing the effectiveness of dialysis and transplantation as treatments for end-stage renal disease, conducted by the National Institute of Allergy and Infectious Diseases (NIAID).

Data were collected from Health Care Financing Administration records of about 93 percent of the U.S. population with end-stage renal disease who received transplants or dialysis between January 1, 1977 and December 31, 1980.

Depending on age at the time of transplantation, about 8-20 percent of transplant patients with grafts from unrelated donors died in the first year; in subsequent years the death rate remained constant at about 2.5 to 5.5 percent per year. (Survival rates doubled for patients receiving kidneys from related donors.) However, mortality rates for dialysis patients remained constant at about 4-21 percent per year, again depending on age.

Results of the analyses were published in the June 30 issue of *The New England Journal of Medicine.*

- Researchers at Beth Israel Hospital in Boston, under a grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), have developed a new experimental method for administering insulin to diabetics—by nasal spray.

Studies on administering insulin by inhalation have been taking place for some time. The results achieved at Beth Israel, however, mark the first time that appropriate serum insulin levels have been reached using this technique.

A mixture of insulin and bile salt (deoxycholate) as a transport medium was administered through a simple nasal spray applicator to both insulin-dependent (Type I) and noninsulin-dependent (Type II) diabetics and to normal controls. The mixture was absorbed effectively, producing a prompt increase of insulin in the blood and corresponding decrease in levels of blood glucose.

The technique is still being developed and will not be available for clinical use for some time, but inhaled insulin may eventually replace some of the daily injections needed by the nearly 11 million diabetics in the U.S.

- Studies supported by the National Institute of Dental Research (NIDR) have shown that persons with insulin-dependent diabetes mellitus (IDDM) are prone to a rare form of periodontal disease.

Researchers at the State University of New York at Buffalo believe that this type of periodontal disease may be caused by a defect in the neutrophils, white blood cells that normally protect gum tissue by rapidly destroying harmful bacteria. In IDDM however, the neutrophils migrate more slowly toward the bacteria, then ingest fewer of the microbes than they normally would. This flaw in the body's natural defense mechanism leads the way to the development of periodontal disease in these patients.

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

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Building 31, Rm. 2B-10
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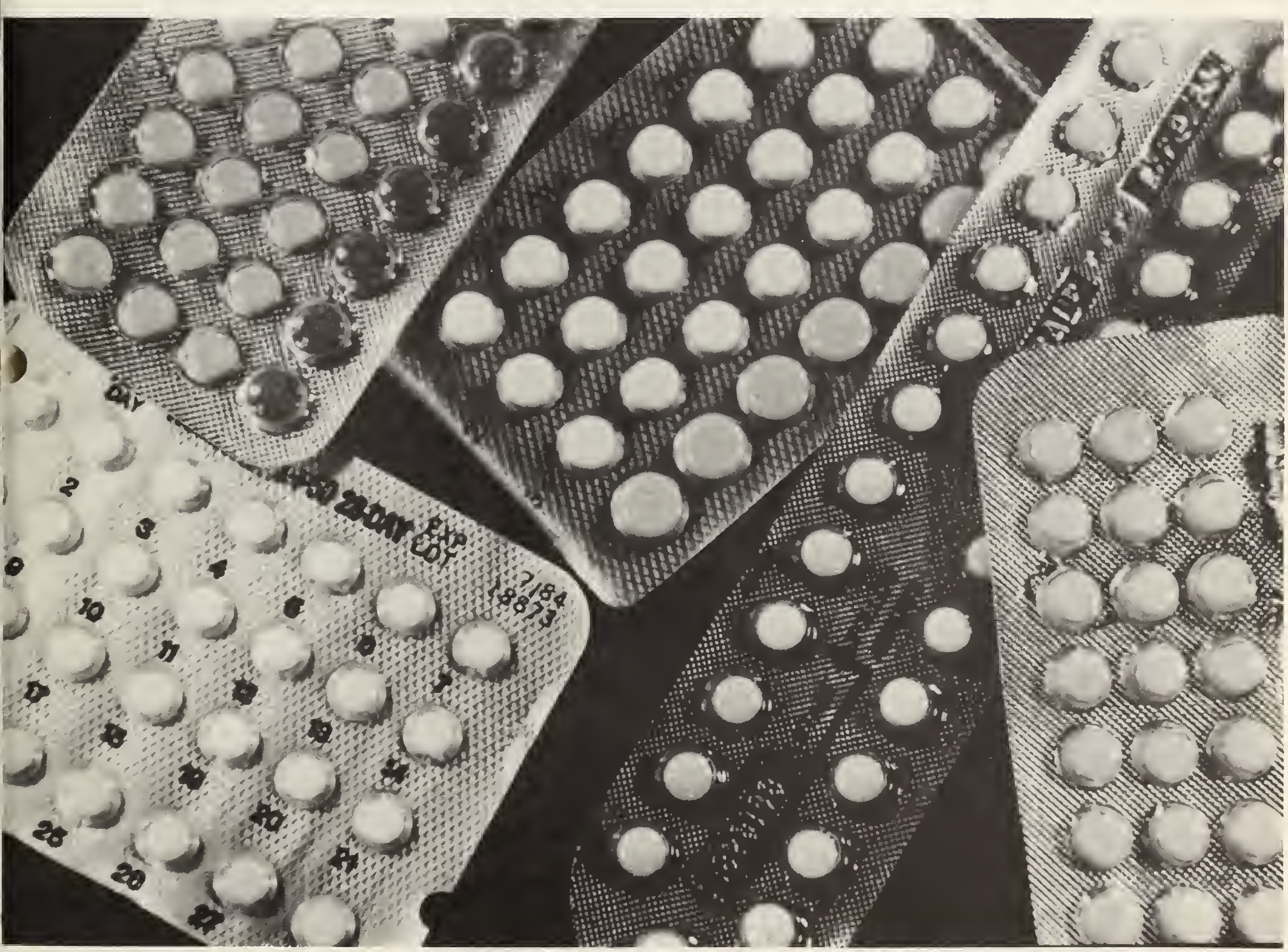

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News&Features
from NIH

August 1983

A study supported by the National Institute of Child Health and Human Development (NICHD) has found that women who take oral contraceptives are no more likely to develop benign tumors of the pituitary gland than women who do not. A link had been suspected because the rise in incidence of pituitary tumors appeared to parallel the rise in pill use.

This study, the largest undertaken on the subject, was designed to investigate whether synthetic hormones in the pill might cause a type of pituitary tumor called prolactinoma. But researchers found that even pill use for five years or more did not lead to an increased risk of developing this tumor.

Further research is needed, however, to determine whether using the pill can aggravate a preexisting prolactinoma. See page 9

A study funded by NIMH shows that depression in children can be as severe and chronic as in adults.

The study is on-going, and so far the investigator has studied 85 depressed children between 8 and 13 years of age. She found that major depressive episodes can last as long as nine months, and that the disorder known as dysthymia, predicts the likelihood of subsequent major depression. See page 6

NHLBI recently released statistics on heart attacks and their victims. The Framingham study noted that men married to women with advanced education were most likely to suffer from heart attacks.

They found that these men were mostly type A personalities, and their spouses tended to work outside of the home after securing advanced educational degrees. See page 10.

Several DRR staff members were on hand to help Institute-supported General Clinical Research Centers celebrate 20th anniversaries this year.

DRR supports 74 centers throughout the United States, by providing a special 8-bed nursing unit, equipped with a metabolic diet kitchen, conference and examination rooms, nursing station, and an area designed to treat outpatients. See page 2.

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Editorial Staff

Mary Donovan
Editor

Susan Gerhold
Associate Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

H News Branch
ilding 31, Room 2B-10
Bethesda, Maryland 20205

Phone:
(301) 496-2535

NIH's GCRCs Celebrate their 20th Anniversaries

Marti Asner

When British scientist James Lind tested oranges and lemons against scurvy on sailors aboard the H.M.S. *Salisbury* in 1747 using matched controls, he was conducting an experiment in a field of medicine today called clinical research. More than two centuries later, Dr. Charles Y. C. Pak, professor of internal medicine at the University of Texas Southwestern Medical School, completed 15 years of clinical research on a drug that will help prevent the formation of a common kidney stone in thousands of sufferers. Even though both men sought answers to the mystery of disease through clinical research, Dr. Pak enjoyed the advantage of access to a federally funded General Clinical Research Center, (GCRC), a freestanding hospital unit which provides sophisticated facilities for clinical investigators.

The first 12 GCRCs were opened in 1960 after Congressional approval and a $3 million appropriation. Now, nearing its 25th anniversary, the GCRC Program, which is administered by the NIH Division of Research Resources (DRR), funds 74 such units, on which more than 3,000 protocols are conducted. It is in one of these research units that Dr. Pak and his research team tested the effectiveness of their kidney stone treatment.

Clinical research is a scientific research process that frequently begins in the laboratory where scientists conduct the basic bench science that lays the foundation for future investigation. Laboratory findings are then tested in animals so researchers can observe the effects of a treatment or drug in the framework of a complete biological system. When the research community is satisfied with both the safety and benefit of their experiment on animals, then human trials can begin.

Human research demands complex care and treatment within a specialized environment where protection of volunteers is of paramount importance. General hospital wards cannot cope with the exacting demands of most research projects; a separate, controlled environment is needed. Therefore, GCRCs were created to fill this need

Dr. Charles Y.C. Pak conducts research on kidney stones at the NIH-supported GCRC University of Texas Southwestern Medical School.

NIH PHOTO 1905

A technician in the diet kitchen weighs and measures most of the food and liquids consumed by research volunteers. Precision and control in patient diets are usually critical to accurate clinical research results.

NIH PHOTO 1906

One of the hallmarks of this specialized environment is the diet kitchen. Almost nowhere in clinical research is precision and control more seriously sought after than in patient diets. Unlike patients elsewhere in the hospital, in many clinical center studies everything the patient consumes is measured for weight, chemical composition, and caloric value. Patients must eat every morsel of food and drink, sometimes even using a spatula to scrape up the last crumb. With intake so tightly controlled, the research team can assume that any changes in a person's metabolic balance is related to the disease, a medical procedure, or medication, and not to nutrition.

The core laboratory in clinical research centers is also unique. Here, special tests and analyses are performed with speed and accuracy, using the most soph[illegible]cated instruments available. Routine tests are handled by the hospital's standard laboratory, freeing the core laboratory for more specialized work.

Dr. Charles Glueck samples food made from the experimental cooking substance sucrose polyester, which holds promise as an effective weight loss agent.

With Dr. Glueck are Elizabeth Hogg (center) and Charalee Allen, nutritionists at the University of Cincinnati General Clinical Research Center, where sucrose polyester recently underwent clinical testing.

Dr. Glueck is the director of the center, which is one of 74 units funded by DRR.

NIH PHOTO 1907

Other than a dedicated diet kitchen and the core laboratory, a Clinical Research Center physically resembles a typical modern hospital unit with an average of eight beds, examination rooms, a nurses' station, a conference room, and, at many centers, an outpatient area where some of the studies can be conducted allowing patients the freedom to return home after therapy. It also provides a great savings to the patient, because they do not have to be hospitalized.

Heading the effort is the chief administrator, also called the principal investigator. This individual oversees the operation of the GCRC grant and is responsible to the NIH for research conducted at the Center. The day-to-day supervision of the Center is the program director's job. The program director must be familiar with all research protocols, direct the core laboratory and metabolic kitchen, and teach the concepts of clinical research to fellows, residents, interns, medical students, and paramedical personnel.

Support staff includes nurses, dietitians, and technicians who are not only trained in patient care, but also specially prepared to carry out the exacting demands of research.

The center's facilities are available to any clinician practicing at the host institution. Usually, the research of these clinicians is supported by the NIH. Proposed research projects are submitted by a clinician to a Center advisory review committee that reviews the scientific merit and potential benefit of the protocol. The Institutional Review Committee looks at the ethical issues.

These ethical considerations usually relate to the patient research volunteers involved in the studies. Before the study begins, patients or normal controls must indicate that they understand the project and any risks involved. Each research volunteer then becomes as much a part of the research team as the clinician or support staff.

When the right blend of people and facilities come together, then a clinical research center can be on the front lines of clinical advances. Such was the case last year when investigators at the University of Cincinnati Medical Center reported on a substitute for fat that contains no calories. The fat substitute, called sucrose polyester, can also lower blood cholesterol and triglycerides, thus reducing the chance of heart disease.

The most recent weight loss study that led program director Dr. Charles J. Glueck and his team to this discovery involved 10 obese men and took seven weeks to complete.

"The NIH-funded Clinical Research Centers provide a perfect environment for studies like this, where we have taken obese but otherwise healthy people and put them in a hospital unit to participate in a complex study," said Dr. Glueck. "The study required a minutely controlled metabolic kitchen run by research-oriented nutritionists. It also required a nursing staff skilled in research techniques, as well as patient care, and a laboratory with a high degree of quality control," he added.

Although GCRCs are ideally suited for metabolic studies, other examples of biomedical research achievements that have taken place at GCRCs highlight the breadth of medical disciplines using these unique facilities. Investigators have:

- Improved hemodialysis treatment and renal and liver transplantation techniques.
- Developed a new diagnostic test for early detection of thyroid deficiency.
- Created a hormone treatment that prolongs life in patients with osteogenic sarcoma.
- Uncovered new reasons why patients with sickle cell anemia are susceptible to bacterial infection.
- Developed a new approach to the dietary treatment of several life-threatening inborn errors of metabolism.
- Devised new surgical therapies for congenital anomalies of the biliary system.

The core laboratory in a GCRC provides special tests and services not readily available elsewhere in the hospital. NIH PHOTO 1908

continued on next page

- Perfected a technique that allows chemotherapy for malignancies to be delivered on a continuing basis directly to the affected organ.

Today's clinical research centers are built on an approach to science that began in Paris in the mid-19th century. Physicians and students from all over the world flocked to the Paris Hospital School to observe clinicians use the experimental methods as applied to physiology. This approach to research established the first principle for all future studies in clinical investigation, namely, that each experiment requires a control.

The most well-known of these early investigators was Dr. Pierre-Charles-Alexandre Louis, often called the "ancestor of the full-time clinical investigator." Louis collected thousands of case histories and autopsy records and kept detailed records on lifestyle and family history. His autopsies were done with painstaking thoroughness, setting a new standard of excellence.

In the later half of the 19th century, German advances in pathology lit up the medical world. At least 20 laboratories and hospitals devoted to research and training sprang up across the country. These schools encouraged students and faculty to compete with each other and then transfer to another university and absorb new ideas. In this open-ended style of learning, new methods of investigation were developed, including the use of chemical and microscopic analyses. Soon every clinic in Germany had its own research laboratory.

In America at this time there were no clinical research laboratories, no training programs in research methods, and no career opportunities for the clinician who might develop an interest in research. But as the country became more industrialized and money became available for philanthropic purposes, medical statesmen set out to make some changes.

Post-graduate training opportunities in medical research started to flourish along with the establishment of the first research laboratories in America. Accomplishments in science soon followed, and by World War I, American physicians and scientists no longer migrated to Germany to study under the reknowned clinicians. Another important influence on clinical science was the American Society for Clinical Research, an organization where young scientists could exchange ideas and work together to set clinical research standards.

From 1908 to 1935 clinical research units, funded by industry and foundations, sprang up. The first and foremost of these was the Hospital of the Rockefeller Institute, which opened in 1908. Throughout the years, this Center made tremendous contributions in the study of physiology, biochemistry, and molecular biology.

Normal volunteers participate in an insulin secretion study at Vanderbilt University Medical Center in Nashville. This outpatient study, along with others, was introduced to the GCRCs in 1971 as a means of expanding clinical research at reasonable cost.
In 1982, the number of outpatient visits was more than 100,000. NIH PHOTO 1909

Five years after the Hospital of the Rockefeller Institute broke ground, Bellevue Hospital opened its first clinical research unit. Research at Bellevue showed that the body surface area was a much more appropriate reference standard for metabolic processes than was the body weight, which had previously been used for such a standard.

In the succeeding decades, clinical research units dotted the map. Landmark studies, such as the one at the University of Michigan, established that the first law of thermodynamics, that of conservation of energy, applies to humans as well as to the rest of creation. The Mayo Clinic in Minnesota opened a nutrition unit and studied the effects of diabetes mellitus on humans. At Massachusetts General Hospital, researchers developed principles of clinical investigation which became the "bible" for metabolic balance studies.

A major boost to clinical research occurred in 1953 when the NIH opened the Clinical Center in Bethesda, Maryland. Ann Reimer, the first chief research dietitian, was brought from the University of Michigan; Russell Wilder came from the Mayo Clinic to be the first scientific director of the Arthritis Institute; noted endocrinologist Dr. Frederic Bartter came from Massachusetts General Hospital along with research dietitian Merme Bonnell. Together these early pioneers founded the first metabolic unit at NIH and the first patient was admitted to the Clinical Center. To make clinical research available to medical science on an even wider scale and to increase the number of trained investigators, the General Clinical Research Centers program was created seven years later.

Earlier this year, the newest GCRC was dedicated at the University of Texas Health Science Center in San Antonio. This is the first center located in a Veterans Administration hospital. Situated on the 7th floor of the Audie L. Murphy Memorial Veterans Hospital, the 10-bed center will study drugs used in the treatment of cancer, high blood pressure, heart disease, depressive and manic illness, liver and kidney diseases, infectious diseases, and neuromuscular diseases. These diseases are of special concern to the Veterans Administration in the care of older veterans.

Most major medical advances in the treatment of disease over the last two decades have stemmed from research done in clinical research centers. There is little doubt that these meccas of learning will continue to supply us with more knowledge about disease. When asked to pinpoint the GCRC Program's key to success, Dr. Myron Genel, GCRC program director and professor of pediatrics at Yale University, summed it up this way: "The code word is stability. We're providing a stable environment within our high-quality medical centers of physical facilities, human resources, laboratory resources, and money.... I daresay that without the research center program, I doubt very much if any of the studies that led to the development of the insulin pump would have been possible. We eventually would have gotten there, but I can tell you that we got there directly because there was a storehouse of informa that had been built up from studies done in clinical research centers." ■

NIMH Scientists Find Anger Leads to Heart Disease

Judy Folkenberg

"Warning: The Surgeon General has determined that anger is dangerous to your health," might be the warning label attached if emotions came in packages.

Three different studies—one, among a group of physicians 25 years after graduation from medical school; another, among patients undergoing diagnostic tests for coronary heart disease; and, a third, among male workers at Western Electric—show that angry people are more prone to coronary heart disease.

Further, anger (as determined by how high one scores on the hostility (HO) scale of the Minnesota Multiphasic Personality Inventory (MMPI) test) appears to play a role in deaths from other causes, according to three Duke University researchers, John Barefoot, W. Grant Dahlstrom, and Redford Williams. "A striking unexpected result emerged from the data from our study of physicians. Routine examination of HO scores for deceased subjects revealed that the scores predict subsequent mortality from all causes as well as they predict coronary heart disease."

And researchers at the Western Electric Company discovered that the relationship between mortality and high HO scores was independent of baseline smoking status, cholesterol, blood pressure, and alcohol use.

Earlier research has shown that type A behavior (including such characteristics as competitiveness, impatience, excessive drive, and hostility) is associated with an increased risk of coronary heart disease. Williams, a National Institute of Mental Health (NIMH) grantee, emphasized that it is now necessary to refine the concept of type A behavior, and discover which characteristics affect the heart and to what degree.

Williams and his colleagues also studied 424 patients who underwent diagnostic testing for coronary heart disease, and discovered "a significantly greater proportion of type A patients had at least one artery with a significant occlusion (blockage) of 75 percent or greater." However, an even larger percentage of those who scored high on the hostility scale—whether they were type A or not—showed a greater rate of coronary heart disease than those who scored low on the scale. Thus, "Hostility score emerged as more strongly related to atherosclerosis (blocked arteries) than type A behavior pattern," says Williams.

The scientists further discovered that those with high HO scores endorsed the assumption "that people in general are going to behave towards others in ways that are mean, selfish, and exploitative." These high scorers also felt that, when people act in a reprehensible manner, they should be punished either physically or verbally.

According to Williams, "What we probably are really measuring is a personality trait, mistrust, but anger is the mechanism or symptom that is obvious and more measurable."

Carrying this premise one step further, Williams concludes that people who do not experience constant mistrust and subsequent anger may enjoy a protective advantage which guards against ill health.

Japan provides strong evidence for this notion. The Japanese traditionally emphasize the importance of group membership over individual aspirations, and they embrace the Japanese concept of "Amae," which means "depending and presuming upon the benevolence of others toward one." Japan also has the lowest incidence of coronary heart disease of any industrial nation.

Various researchers have chronicled an increasing rate of coronary disease among the Japanese living in California. This trend has been attributed chiefly to the immigrants' abandoning traditional Japanese cultural values in favor of American lifestyles.

Williams has been able to test the hypothesis that the Japanese benevolent view of others is an important protective element against heart disease. In a study soon to be published in a Japanese medical journal, the hostility scale of the MMPI test was given to a group of Japanese. Far more Japanese had lower hostility scores than their American counterparts. ■

Investigators Warn Women Not to Use IUDs While Breast Feeding

Maureen Gardner

Women who have an intrauterine device (IUD) inserted when they are lactating run an increased risk that the IUD will perforate the uterus. This conclusion comes from a report of the Women's Health Study, a large project started in 1976 by the National Institute of Child Health and Human Development (NICHD).

Uterine perforation happens rarely in IUD users. It can be serious, however, if the IUD must be removed through abdominal surgery. For the Women's Health Study, researchers in 16 major U.S. hospitals collected information on women admitted for uterine perforation and other serious complications of IUD use.

In this report, investigators Steven Heartwell of the University of Texas Southwestern and Sarah Schlesselman of George Washington University in Washington, D.C. evaluated 32 women who were hospitalized for abdominal surgery to remove an IUD. The researchers compared the medical histories of these women with those of 497 other IUD users who did not have uterine perforation.

They noted that all but one of the surgery patients were mothers of at least one child. While other studies have shown that mothers in general have a greater risk of perforation, the present study found that the risk is not evenly distributed. Drs. Heartwell and Schlesselman discovered that within the group of mothers, those who were lactating when they had an IUD inserted were ten times more likely than the others to suffer uterine perforation requiring surgery.

The type of IUD did not appear to influence the risk of perforation. In addition, for the women who started using IUDs following childbirth, the timing of insertion did not change the risk of perforation. Those who had IUDs inserted within two months after delivery were no more likely to experience perforation than those with later insertions.

According to Dr. Heartwell, two main factors may increase the risk of perforation in lactating women. The walls of the uterus remain thin in breastfeeding women because lactation keeps estrogen levels low. And breastfeeding stimulates the uterus to contract rapidly to its pre-pregnancy size, which may make it easier for an IUD to perforate the uterine wall.

The researchers emphasize that although this study shows an increased risk of perforation in lactating women, the actual number of uterine perforations is small. They note that for this study, a 20-month search of 16 hospitals found only 32 cases of uterine perforation requiring surgery.

Drs. Heartwell and Schlesselman also studied the cases of 106 women who were hospitalized because their IUDs had gradually become embedded in the wall of the uterus. Those who were lactating when the IUD was inserted were twice as likely as the others to be hospitalized for this complication.

"Until other studies confirm these findings, we think it is too soon to recommend that IUDs not be used by lactating women," said Dr. Heartwell. However, based on their findings, the researchers warn clinicians to "exercise special caution" when inserting IUDs in lactating women. ■

Depression in Children Found to be as Serious as for Adults

Marilyn Sargent

- Major depressive disorder—a serious illness manifested by mood, eating, and sleeping disturbances, and often by suicidal behaviors—is readily detectable in children between 10 and 12 years of age, and is similar in severity and chronicity to the disorder in adults.
- Dysthymia, a condition less severe than major depression but far more prolonged, starts earlier—typically between 7 and 8 years of age—and is "a strong predictor of children at risk for subsequent major depression."

These disorders were recently investigated in an on-going study of depressed children. The study is supported by the National Institute of Mental Health (NIMH).

Reporting on her findings, Dr. Marica Kovacs, associate professor, Department of Psychiatry, Western Psychiatric Institute and Clinic in Pittsburgh, acknowledged that before the study she thought childhood depression to be milder and less chronic than depression in adults. "Now I see similarity in patterns."

Among findings that surprised Kovacs were:

- Major depressive episodes in children last close to 9 months on the average. Kovacs found only a 17 percent recovery rate at 3 months and 44 percent at 6 months. By 18 months after disorder onset, 93 percent had recovered (2 months free of significant symptoms). The remaining 7 percent have not gotten better during the 5 years that the study has been in progress, said the researcher.
- Major depression proved more chronic in children than expected. Within 6 months of the first episode's remission, 17 percent had another episode. By 12 months, 22 percent had a recurrence, and within 2 years, 44 percent of the children experienced a second full-blown major depression. A number of the children have had several episodes since the study began, said Kovacs.
- Dysthymia is even less remitting than major depression. After 2 years of continuous symptoms (1 year of continuous symptoms are required for diagnosis), only 16 percent of the children recovered compared to the 93 percent recovery rate for major depressive episodes. The average length of continuous dysthymia is 3 years and the highest recovery rate—80 percent—occurs after 5 years of symptoms.
- When following the course of dysthymic children over a 5-year period, 73 percent will develop their first episode of major depression, "superimposed on the dysthymia. Eventually a few of the children go on to develop mania," said Kovacs. She considered dysthymia to be the leading factor in identifying children at risk for affective disorders.

Up to this time, the investigator has studied 85 depressed children between 8 and 13 years of age, stringently diagnosed over a 4- to 6-month evaluation period by Diagnostic and Statistical Manual III criteria. To be accepted for the study, children have to meet criteria for at least one of three depressive diagnoses: major affective disorder, dysthymia, or adjustment disorder with depressed mood.

With the exception of those with adjustment disorder, at least 80 percent of the children have multiple disorders, some having as many as five diagnosable conditions, said Kovacs. Thirty-eight percent with major depression have underlying dysthymia and 50 percent of dysthymic children have symptoms of major depression.

Anxiety disorder, the most common concurrent diagnosis for all three depressive groups, had no effect on recovery rates and appeared associated with decreased risk of a second episode of major depression.

In contrast, underlying dysthymia placed children with major depression at greater risk for repeated episodes. Thirty-six percent of "double-depressed" children had a second episode 4 months after remission compared to only 6 percent of "single-depressed" kids. This chronicity and perniciousness is similar to that found in double-depressed adults by investigators in the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression.

Children who had adjustment disorder with depressed mood were relatively lucky. They recovered more rapidly and completely—90 percent by the end of one year. None developed dysthymia or major depression.

The researcher examined various phenomena that might be associated with recovery from the initial bout of a depressive disorder; e.g., sex of the child, age of onset of the disorder, whether the child was receiving treatment. Only age of onset was clearly and unequivocably associated with recovery—the earlier the onset the later the recovery.

A search for developmental influences that might mediate depression "failed to verify salient developmental hypotheses. . . . Regardless of developmental stage, these kids have problems with school and with peers," said Kovacs. "We have to figure out how to teach them to cope and we must provide more efficacious treatment."

Kovacs' study also includes an age-matched, non-depressed, psychiatrically diagnosed comparison group. The most common conditions found in this group are attention and conduct disorders.

Only one demographic factor differentiated the two groups—sex ratio. Th depressed group had equal numbers boys and girls in contrast to three boys f every girl in the "mixed diagnosis" gro Both cohorts were characterized b a high prevalence of deprivation, poverty, and large numbers of parental figures. Only 30 percent lived with both biological parents.

High divorce rates and low socioeconomic status appear to be typical of children with problems and not related to a specific disorder, Kovacs pointed out. Neither is the presence of "rejection," a condition often thought related to the development of depression. "I looked at potential indices of rejection and found no differences between the two groups."

Kovacs cited the need to replicate her findings, particularly regarding the relationship of early dysthymia with later major affective illness. This finding has major importance in terms of intervention and prevention. Also, the development of appropriate helping programs for depressed children is of utmost importance, she concluded. ■

NIAID Researchers Create Potential Live, Recombinant Virus Vaccine

Patricia Randall

Scientists at the National Institute of Allergy and Infectious Diseases (NIAID) have combined vaccinia virus, used to immunize against smallpox, with genetic material from hepatitis B virus to produce what may be the first of a new generation of live, recombinant vaccines. The hybrid vaccinia virus contains the gene for hepatitis B surface antigen and stimulates protective antibodies against hepatitis when injected into animals.

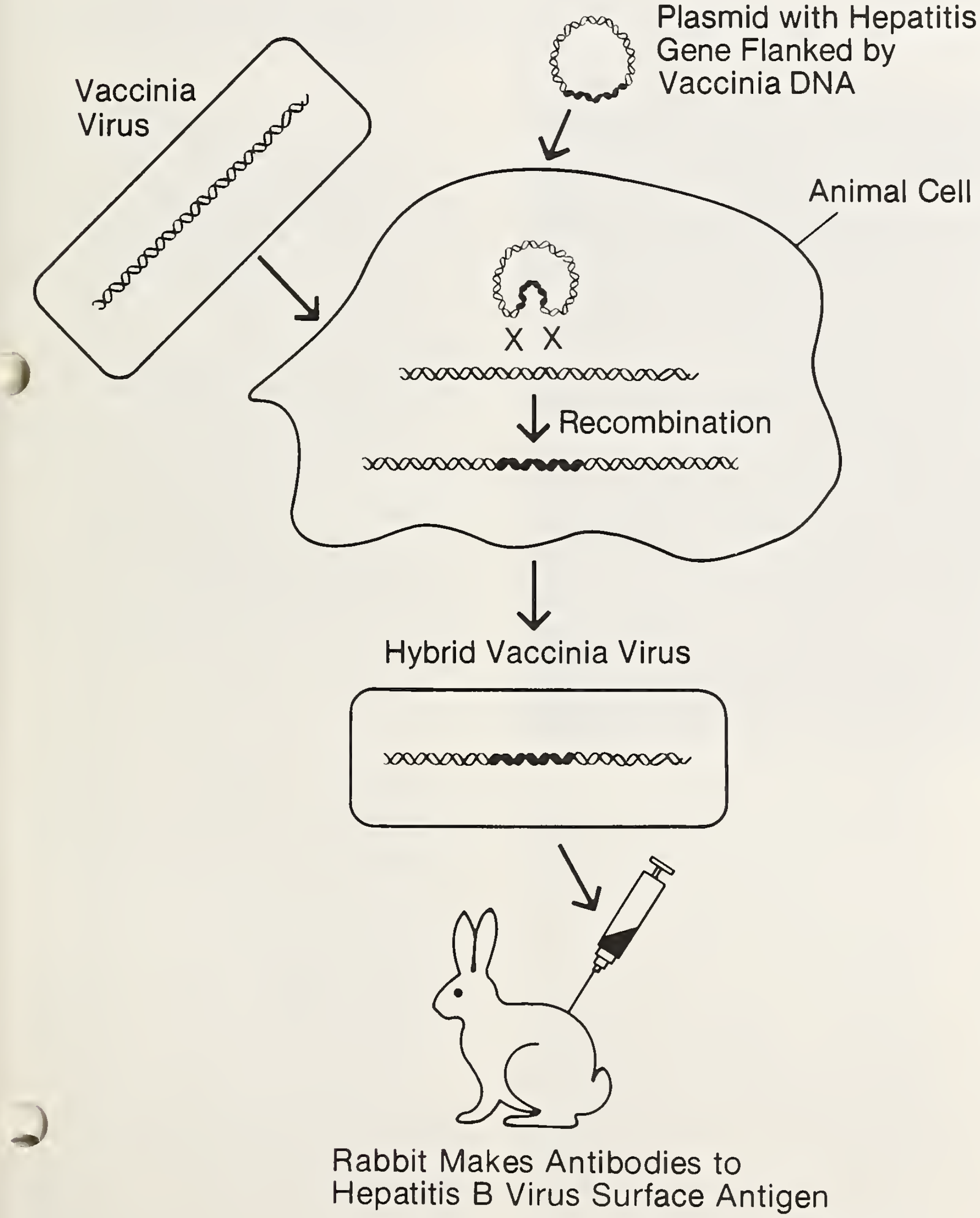
NIAID researchers Geoffrey L. Smith, Michael Mackett, and Bernard Moss have identified sites on the vaccinia virus genome at which foreign DNA can be inserted without the virus losing infectivity. They have also devised a way to introduce foreign DNA into the virus so that the protein encoded by the new DNA is produced along with normal vaccinia protein during the growth cycle of the virus. The investigators anticipate that this technique could be used to insert genes for antigens of various disease-causing agents and to make a number of different live vaccines.

In a study recently reported in *Nature*, the scientists used the gene from hepatitis B virus that directs production of the antigen. They hooked the hepatitis antigen gene to the specific pieces of vaccinia DNA that are required to make it active, and inserted this modified gene into an independent segment of genetic material called a plasmid. Next, they infected cells with the plasmid and with regular vaccinia virus. During replication in the cell, the modified hepatitis gene took the place of certain, known marker genes in the vaccinia virus. The investigators then identified and recovered the hybrid virus that contained the hepatitis gene.

When the hybrid virus was injected into rabbits, it produced a local reaction to vaccinia virus and stimulated significant amounts of antibody to hepatitis antigen. In humans, equivalent levels of antibodies would provide protection against hepatitis B virus infection. Further studies are underway to increase the amount of antigen produced by the hybrid virus as well as to measure safety and effectiveness of the virus in other animals. If these tests are successful, human studies can be planned.

Dr. Moss and his colleagues are optimistic that this new type of recombinant virus shows promise for use as a less costly and more easily administered hepatitis B vaccine than the one now available. The vaccinia virus, given in one inoculation, has already proved itself in the successful campaign to eradicate smallpox. An effective recombinant vaccinia virus would be ideal for mass immunization campaigns, particularly for children in Asia and Africa, areas where hepatitis B is a serious and widespread problem. Worldwide, an estimated 200 million persons have chronic hepatitis B, and many die from acute liver disease, cirrhosis, or liver cancer.

The present hepatitis B vaccine is made from an antigen harvested from the blood of persons with chronic hepatitis B. Using expensive and complicated procedures, the antigen is separated from other blood factors, purified, and chemically inactivated before it is made into a vaccine. Two, or in some cases three, doses of the vaccine provide safe and effective protection. However, the cost and the required multiple doses may make this vaccine impractical for general immunization programs, particularly in developing countries. ■


Plasmid with Hepatitis Gene Flanked by Vaccinia DNA
Vaccinia Virus
Animal Cell
X X
Recombination
Hybrid Vaccinia Virus
Rabbit Makes Antibodies to Hepatitis B Virus Surface Antigen

NIH PHOTO 1910

NCI Focuses Attention on Cancer and Minorities

Harriet Page

Over the past decade, the Field Studies and Statistics Program of the National Cancer Institute's (NCI) Division of Cancer Cause and Prevention has been generating national statistics on cancer incidence, mortality and survival.

Just two years after the passage of the National Cancer Act in 1971, the NCI established its Surveillance, Epidemiology and End Results program, known as the SEER program. This is a system of population-based cancer registries located in various parts of the country, designed to monitor cancer incidence and survival on a national basis. Such data provide signals for further epidemiological studies and for monitoring the progress of the National Cancer Program.

As originally set up, the SEER program represented within the American population: 10 percent of whites, 9 percent of blacks, 5 percent of Hispanics, and 30 percent of other minority groups, including American Indians, Japanese and Chinese. The NCI has also been gathering data on incidence and mortality that delineate cancer patterns among various ethnic groups and geographic areas.

NCI published several publications on statistics within the last 10 years, providing valuable clues for investigators everywhere. A few of the studies completed, or planned, include:

Analytical studies, usually case-control in nature, to pinpoint the environmental and host factors that account for differences in cancer risk among various ethnic groups in certain areas of the United States. In both the intramural and extramural programs of NCI, studies are under way to clarify the reasons for elevated cancer rates in blacks. These include cancers of the lung, stomach, and pancreas in southern Louisiana; cancer of the pancreas in Los Angeles and Baltimore; cancer of the lung in Texas and New Jersey; and prostate cancer in Los Angeles and other areas. NCI is also coordinating a multicenter study of cervical cancer.

- An NCI study carried out with Howard University showed that nutritional deficiencies and alcohol consumption helped account for the high rates of esophageal cancer among black men in Washington, D.C.
- In collaboration with Dr. John Berg, an epidemiologist and pathologist at the University of Colorado, detailed analyses of the SEER data are helping to delineate the ethnic patterns of cancers by site and cell type. To make incidence and survival data more precise, NCI is striving to obtain sharper population estimates for minority groups.
- Collaborative studies with investigators in China are helping to clarify the cancer experience of Chinese populations in parts of China and in other areas of the world, including the United States.

One of the most pressing concerns is the discrepancy in survival between whites and blacks in the United States. NCI data have shown that for cancer patients diagnosed between 1955 and 1964, survival rates for 16 of 18 selected cancer sites, 11 stages combined, were higher for whites than for blacks.

Data from the Veterans Administration on patients diagnosed and treated during the years 1958-1963 show that the white survival advantage for urinary bladder cancer persisted even when all aspects of treatment were the same.

More recent data from NCI for patients diagnosed during the years 1964-73 yield further evidence of the differences in black/white survival. Even after adjustment for age and stage of disease, five-year survival rates among blacks were at least 10 percent lower than those among whites for cancers of the colon, rectum, and urinary bladder, and for Hodgkin's disease, in both men and women.

For black women, five-year survival rates for breast cancer and cancer of the uterine corpus were lower than for white women. For black men, survival rates for cancer of the larynx, prostate, and kidney are lower than for white men. Survival differences of less than 10 percent, still statistically significant, and still favoring whites over blacks, are evident for cancers of the lung and bronchus in both men and women, and for the uterine cervix in women.

To address this problem and to identify why these serious differences in survival exist, two NCI divisions are planning a prospective study. A variety of factors will be looked at in addition to stage and age. The Division of Cancer Cause and Prevention and the Division of Resources, Centers, and Community Activities are contributing jointly to the four-year, $1.7 million study. Proposals have been received and NCI expects to award contracts for specimen and data collection by fall 1983 and spring 1984.

Four major cancer sites will be studied: breast cancer and cancer of the uterine corpus in women, and cancers of the colon and urinary bladder in both sexes. Data will be collected from medical records, pathology reports, and patient interviews.

Information will be sought on what brought the patient to a physician, reasons for any delays in seeking treatment, family history, other illnesses, prior estrogen use, socioeconomic indicators, diet and smoking patterns, and alcohol use. Thus, this study will be looking into such factors as host vulnerability, lifestyle, and utilization of the medical system—factors far beyond those gleaned from retrospective studies of medical records.

During 1979, one of the SEER registries ceased its participation, leaving Hispanics and blacks underrepresented. NCI hopes to award a contract, by September 1983, to establish a SEER registry in a population "of at least 300,000 blacks and 300,000 Hispanics." Six areas in the United States will qualify: Los Angeles County, Chicago, New York City, Miami and/or Florida, the State of New Jersey, and the State of Texas or parts of it. Priority will be given to areas in this group that already have historical data.

NCI is also including in the SEER data, in an informal way, information from a cancer registry in Anchorage, Alaska. This registry, which is attached to the Alaskan field station of the Centers for Disease Control, has provided cancer incidence data on Alaskan natives, including Eskimos, Amerindians, and Aleuts.

Some other epidemiological studies in progress, or planned, include:

- Updated maps of cancer mortality for the more common tumors for the 1970s.
- Surveys of groups exposed to occupational hazards that include groups with large numbers of black workers. Among these are dry cleaners, jewelry workers, and tobacco workers. Medical surveillance projects of high-risk workers include a group of mostly black men exposed in the past to beta-naphthylamine, a bladder carcinogen.
- Epidemiologic studies to clarify th shifting patterns of risk among migra ing populations within the United States, and to determine the responsible factors. A collaborative project was developed recently, for example, to determine the patterns of cancer risk among Puerto Rican migrants to New York City. Studies are also being planned to evaluate the influence of migration on the risk of cancers among blacks in Detroit and San Francisco, where SEER registries are located.
- Special studies to discover the reasons for the elevated risks of biliary tract cancer in American Indians and Hispanics; nasopharyngeal cancer in Chinese-Americans and Alaskan natives; stomach cancer in Hispanics and Japanese-Americans; T-cell leukemia in blacks (particularly in the southeastern U.S. and in Caribbean countries) as well as in Japan; salivary gland tumors in Eskimos; liver cancer in Oriental populations, Hispanics and Eskimos; oral cancer in Puerto Rico; and thyroid cancer in various ethnic groups of Hawaii.

As a result of recommendations by th National Cancer Advisory Board, an ternal working group was formed at NCI to strengthen and coordinate NCI programs concerned with minorities. One program, the *Clinical Cancer Education*

Grants provide support for multidisciplinary cancer teaching in schools of medicine and dentistry. Howard University Medical School, Meharry Medical School, and the University of Puerto Rico Medical School are among those that have received institutional grants. The *Minority Access to Research Careers* provides funds for the training of minority scholars in cancer-related areas, and the *Minority Biomedical Support* (MBS) program funds biomedical research in institutions located in areas of minority populations or those that represent land-grant minority colleges. At these medical schools, students receive stipends through these institutional grants. At the Tenth Annual MBS Symposium in Albuquerque in 1982, MBS student researchers presented papers and met with scientists from government and other institutions. The *NCI Minority Outreach Program* employs diverse efforts to attract minority professionals by recruiting at minority institutions and participating in conferences with high minority attendance.

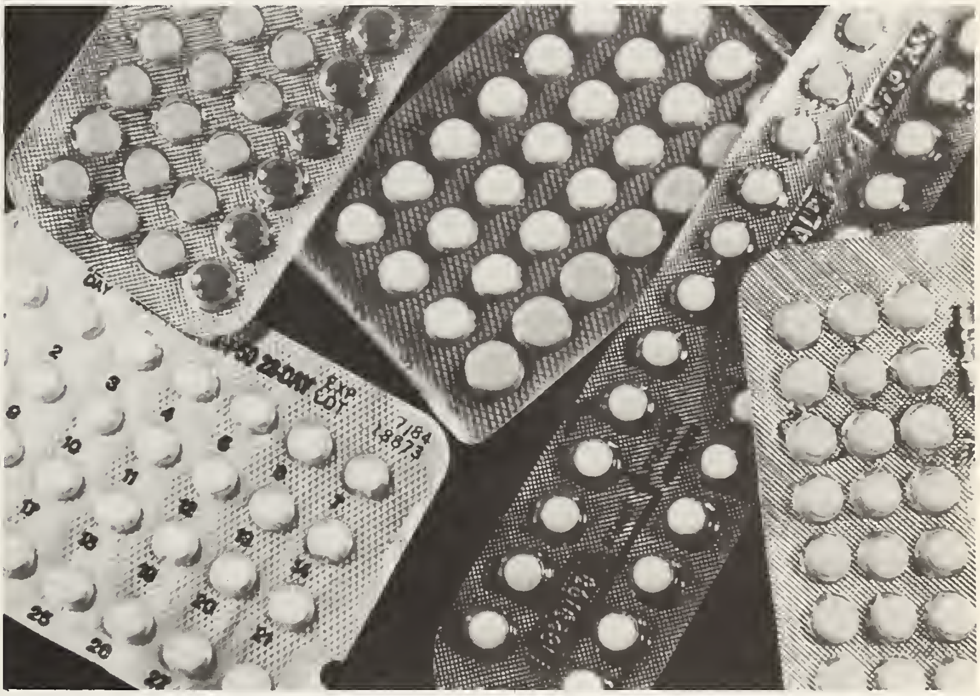
Several initiatives were taken in 1982-1983 by the Office of Cancer Communications. A pamphlet entitled "What Black Americans Should Know About Cancer," first developed in 1977, was evaluated and revised. Public education programs were developed for Hispanics and blacks, with special efforts to reach women and smokers. Steps were taken to revise educational programs dealing with breast cancer among minorities, and cancer news coverage in newspapers and journals for blacks was analyzed to improve techniques for disseminating cancer information.

Special interest in Hispanic groups helped to promote an NCI-supported conference in August 1982 at the Pan American Health Organization in Washington, D.C., involving epidemiologists from various countries in Latin America and areas of the United States where Hispanics are concentrated.

Steps were also taken to strengthen lines of communications between NCI and the American Cancer Society in terms of publications and educational programs for minority groups. ■

Four Medical Centers Find No Link Between the Pill and Pituitary Tumors

Maureen Gardner



A new study has cleared oral contraceptives of a suspected risk: Women who have taken the pill have no increased chances of developing certain benign tumors of the pituitary gland. This is the conclusion of a multicenter project supported by the National Institute of Child Health and Human Development (NICHD).

In the largest study of pituitary gland tumors, researchers in four medical centers in the U.S. and Canada evaluated more than 200 women with prolactinomas. The findings are reported in the June 1983 issue of *Fertility and Sterility*.

According to the new report, doctors have diagnosed greater numbers of pituitary tumors in recent years, especially in young women. Although the tumors are not malignant, they can enlarge significantly and have serious medical consequences. Also, the treatments themselves—surgery or chemotherapy—cause side effects.

Most of these pituitary tumors are prolactinomas, so called because they secrete the hormone prolactin. High levels of prolactin, a hormone that promotes milk production in breastfeeding women, can stop menstrual cycles (amenorrhea) and cause breast secretions (galactorrhea).

In the past, some researchers suspected a link between prolactinomas and oral contraceptives because the growing rates of the disorder seemed to parallel the rise in pill use. In addition, prolactinomas have developed in experimental animals given estrogens. However, the authors noted that it is possible that more prolactinomas are being diagnosed simply because doctors are using new, more precise diagnostic methods, including more sensitive blood tests and radiologic techniques.

The present study was designed to examine the possibility that synthetic hormones in the pill might cause prolactinomas. The research group collected information on women with prolactinomas or possible symptoms of the disorder, such as high prolactin levels in their blood, amenorrhea, or galactorrhea.

They identified three groups of patients: 212 women with confirmed prolactinomas; 119 women with high prolactin levels and amenorrhea, galactorrhea, or both; and 205 women with no signs of pituitary abnormality except amenorrhea, galactorrhea, or both. The researchers then compared the medical and contraceptive histories of these women with equal numbers of healthy women.

The comparisons showed that women who have used oral contraceptives are no more likely than other women to develop prolactinomas, amenorrhea, or galactorrhea. Even women who used the pill for 5 years or more had no increased chances of developing these disorders.

The authors reported that women with pituitary tumors, though no more likely to have taken oral contraceptives, were more likely to have had a history of infertility or menstrual problems. Use of the pill did not add to the chances of developing a prolactinoma in women who had menstrual problems before they started the pill. These findings confirm the results of previous smaller studies.

According to the investigators, however, future research should examine a question that this study was not designed to address—whether use of the pill can aggravate a preexisting prolactinoma. ■

NHLBI Study Notes that Husbands are More Likely to Suffer Heart Attacks if their Wives Have Advanced Degrees and Work Outside the Home

Prepared by the National Heart, Lung and Blood Institute

For many years now, researchers have maintained that married men live longer than do single men. It has been shown that married men have lower rates of coronary heart disease (CHD) than do single, widowed or divorced men, which may help to explain the lower death rate among husbands. However, the latest findings from the Framingham Heart Study, reported in the July issue of the *American Journal of Epidemiology*, indicate that at least some married men may be at increased risk of developing CHD if they are married to women with advanced degrees or employed outside the home most of their adult life. The study was conducted by Drs. Suzanne Haynes of the University of North Carolina, Chapel Hill, Elaine Eaker of the National Heart, Lung and Blood Institute (NHLBI) and Manning Feinleib, formerly with NHLBI.

The Framingham Heart Study subgroup of married couples represented here is a fairly small (269 spouse pairs) and specific population. The mean age for men was 54 years at baseline; the majority were blue-collar workers, had a high school education or less, and the vast majority reported being married only once with a duration of over 25 years; generalizations to other groups must be done with caution. In addition, these data were collected in the mid-1960's and may have limited application today, given changing life styles and wider acceptance of new roles for women.

In general, men married to women with some education beyond high school are more than twice as likely to develop CHD than are men married to women with grammar school educations. The increased risk of CHD among these men was noted only among the husbands of women employed outside the home. For men of type A personality—the hard-driving, time-pressured, ambitious type—the risk of developing CHD is 3.5 times that of the more sedate type B men when both are married to women working outside the home. There is no difference in the rates of heart disease between type A and type B husbands if married to housewives. When the behavior types of both spouses were considered, the highest rates of CHD are found among type A men married to type B wives, among whom 25 percent developed CHD over the ten-year follow-up period (compared with type B men with type B wives, whose rate of CHD is only 7.8 percent). These effects were seen regardless of the husband's occupational status or his other risk factors such as high blood pressure or cigarette smoking.

These conclusions were part of the findings of a ten-year study of spouse pairs to correlate social status, behavior types, educational levels and personality characteristics to the incidence of coronary heart disease among husbands. The Framingham Heart Study has been in progress since the 1950s, and is funded by NHLBI.

Between 1965-1967, an extensive questionnaire designed to measure psychological and social variables was administered to 269 spouse pairs. At that time, the husbands of the pairs were aged 45 to 64 years. The researchers followed the couples for ten years and recorded the development of heart disease among the husbands.

The investigators were especially interested in data that would answer questions relating to the extent to which type A men and type A women form pairs; whether high social status of wives or incongruent social status between the husbands and wives increases the risk of the husband developing CHD or whether certain behavior patterns of the wives correlate with increased incidence of CHD in their husbands; and whether social status or behavior of wives modifies rates of CHD differently among type A as compared to type B husbands.

At the time the men enrolled into the study, their standard risk factors were assessed, including age, cholesterol levels, blood pressure, and number of cigarettes smoked per day. The findings reported here are independent of these factors, however. Educational levels, employment status and occupation of both spouses were recorded, as was the occupation of each person's father. Women who had worked outside the home for more than half their adult lives (defined as the years from age 18 on) were considered working women. Wives who did not fit this definition, even though they had worked at least some of the time outside the home, were classified as housewives. Occupations for both men and women were grouped into three categories: white-collar (professionals, managers, business people), clerical and kindred workers, and blue-collar workers (manual, protective and service workers). It should be noted that women identified as white-collar workers in Framingham during this time period were mostly teachers, nurses, and librarians. In addition to being classified by occupation, the volunteers were placed into educational categories (grammar school, high school, or some college). A majority of spouse pairs, 57.5 percent, fell within the same educational category. In general, about 18 percent of both men and women had a grammar school education, 56 percent had completed high school, and 26 percent had at least some college. Fifty-five percent of the employed couples were found to hold similar occupations; both spouses were classified as white-collar, clerical or blue-collar.

Overall, the results of the study show that a man married to a woman with at least some education beyond high school has 2.6 times the probability of developing heart disease than does a man married to a woman with a grammar school education. If these figures are further refined by looking at rates of heart disease according to the husband's level of education compared with his wife's, the man was at higher risk if married to a woman of higher education, regardless of his own educational level.

The employment status of wives, that is whether working inside or outside the home, was not significantly related to the development of coronary heart disease among the men. The ten-year rate of heart disease for husbands of housewives was 16.1 percent as compared to 15.2 percent for men married to women employed outside the home. When individual categories of occupational status were examined, the results showed that men married to women in white-collar occupations were three to five times more likely to develop heart disease than were men married to women in the blue-collar or clerical categories or housewives, regardless of the men's occupations. Of the 15 men in the study who were married to white-collar women, 7 (46.7 percent) developed heart disease during the ten-year study.

When the combined effect of the wives' education and employment status was correlated with their husbands' rate of heart disease, it was found that the increased risk among men married to women with some education beyond high school was confined to those married to women working outside the home. These men were 7.6 times more likely to develop heart disease than were men married to women with grammar school educations. No association was found between the educational level of women who were housewives and the development of heart disease among their husbands.

Because of the high concordance between spouses for educational level, the observation that men are at excess risk [illegible] developing heart disease if married to women with an education beyond high school and employed outside the home may appear to be contrary to what is observed in the national prevalence rates for coronary heart disease. For persons aged 45-64 years, reported coronary heart disease rates decrease with increased income and education. In the Framingham spouse subgroup, there was no association between the husband's own educational level and incidence of heart disease; although, the rate of disease was slightly higher among blue-collar as compared to white-collar workers. The association of wives' educational level to disease rates among husbands is independent of husbands' educational level, however, it is confined to blue-collar men married to women working outside the home. This suggests that the association reflects more than an effect of social status, per se, on disease occurrence, but rather a more complex interaction between spouses.

The researchers put forth several hypotheses to explain their findings with the suggestion that each be explored in future studies. Among these were the possibility of role conflicts among the women; that is, the dual responsibility of holding a white-collar job and raising children. Or, perhaps, women who worked in high-status jobs outside the home may have threatened their husbands' self-esteem, creating stress in the relationship. It should be noted that although these explanations seem logical and appealing they were not supported in the Framingham analysis. Self selection of high-risk men to marry women of high social status also was ruled out as an explanation. However these possibilities should be examined in larger and more contemporary populations.

Further analysis revealed that highly educated working wives whose husbands developed heart disease were significantly more likely to have had a nonsupportive boss and fewer job promotions than were wives of men who remained healthy. This indicates that it may not be the woman's status per se that is associated with her husband's risk of disease, but perhaps the stressful environment in which she works. The husband may feel sympathy for his wife's stressful job situation, but be helpless to ease her situation. These men who developed heart disease did not report more marital dissatisfaction or marital disagreements as compared to non-cases.

The psychosocial tests administered to the volunteer couples at the beginning of the study included questions to establish personality types (A or B), reaction to anger and so forth. Thus, in addition to correlating the husbands' heart disease with the wives' level of education and occupation status, the spouse pairs could be examined for similarity of personality types of husband and wife and behavioral influences of the spouses that may be involved in the development of heart disease. Type A behavior was defined as the upper 50 percent of scores and type B was the lower 50 percent of scores on the Framingham type A scale for each sex and group aged 45-54 and 55-64 years. One hundred twenty-six men were defined as type A and 135 were defined as type B.

As was expected, type A men experienced nearly twice the likelihood of developing heart disease as did type B men, yet the two groups had similar values for the standard coronary heart disease risk factors. There was a tendency for the type A men to be employed in white-collar occupations and the type B men to have blue-collar jobs, though the difference did not reach statistical significance. Type A men reported more marital disagreements and personal worries than did the type B men, and scored higher on scales to measure tension, daily stress and symptoms of anger and anxiety. No association was found between the husbands' behavior and whether the wives worked outside the home. However, regarding the women who worked outside the home, slightly more of the type A men than type B men were married to women in white-collar occupations, and slightly more of the type B men were married to blue-collar women than were type A men.

Significant differences were found regarding the wives' education as related to the husbands' behavior type. Type A men are more likely than are type B men to be married to women with 13 or more years of education, and the type B men are more likely than type A men to have wives with 8 or fewer years of education. No differences were found in the pairing of the spouses regarding behavior types. That is, type A men and type B men were equally as likely to be married to type A or type B women. Among men married to women with an education beyond high school, the incidence of heart disease among type A men was 2.5 times that of the type B men. The difference in heart disease rates between type A and type B husbands was not apparent if married to women with a high school education or less. Another interrelationship was found between wives' employment status and husbands' behavior type. Type A and type B men had about the same rate of heart disease if they were married to housewives; however type A men were 3.5 times more likely to develop CHD than type B men if both were married to women who worked outside the home.

The researchers initially postulated that having a type A wife may place a type A husband at increased risk of heart disease because of the potential risk that such marital arrangements might have on a husband's sense of control or self-esteem. Contrary to expectation, type A men married to type B women had the highest (25 percent) rate of heart disease in the study, nearly three times the rate of type B men married to type B women. Men, whether type A or B, married to type A wives experienced the same rate of heart disease, approximately 16 percent. It may be psychologically or physiologically taxing for a husband who is hard-driving, competitive and ambitious to live with a woman who is the opposite.

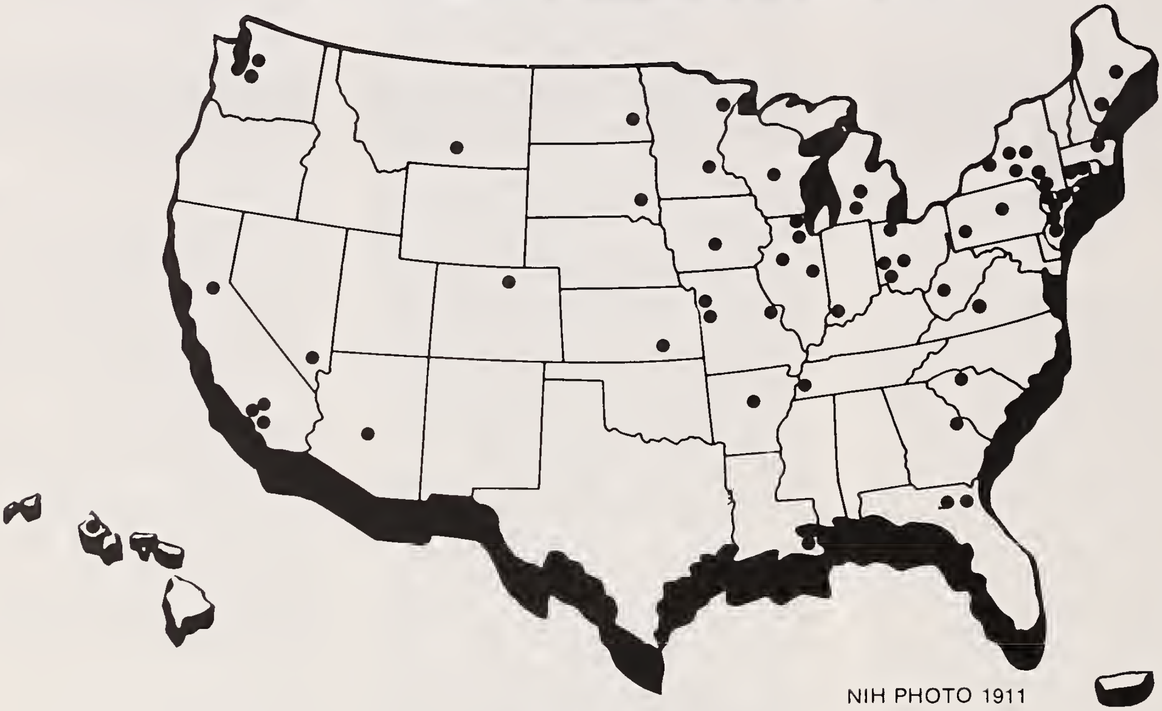
These findings suggest that the effect of type A behavior on the risk of developing heart disease may depend on certain environmental situations, such as spouse characteristics. It is important to note, the researchers say, that this risk modification was most pronounced if the husband was employed in blue-collar occupations. Among white-collar husbands, type A men were at higher risk than were type B men regardless of these characteristics of their wives.

The researchers emphasize that although many of the findings reported here are provocative, the results will be most useful in providing direction for future research in the area of spouse relationships and coronary heart disease. ■

MEDICAL CAPSULES

Sandra D. Levine

Location of Funded CCOPs



NIH PHOTO 1911

• A program which will bring together the expertise of community oncologists with current cancer research studies has been introduced by the National Cancer Institute (NCI).

In this new program, qualified community physicians will participate in clinical trials by affiliating with NCI-supported treatment programs at major medical centers, and national and regional clinical cooperative groups, that conduct large treatment studies.

Fifty-nine groups of hospitals or of physicians in 32 states will participate in the Community Clinical Oncology Program (CCOPs), which is expected to bring over five thousand new patients each year into treatment studies. At least 50 evaluable patients per year (and in many cases more than 100) will be entered by each of the community groups into NCI approved clinical protocols. This will enable effective evaluations of new therapies to be made in less time.

NCI funding is given to each local program through a community hospital or health care organization associated with that program, and patients are treated under the direction of their local physicians.

It is anticipated that the program will make a significant contribution to efforts to improve treatment methods for cancer patients.

Further information may be obtained from the NCI Office of Cancer Communications.

• A study funded in part by the National Institutes of Health suggests that certain patients with growth hormone deficiency might benefit from treatment with synthetic growth hormone releasing factor (GRF). The synthetic GRF may promote growth in children who do not produce enough growth hormone because of a deficiency of GRF, the substance that controls growth hormone release.

Scientists from the National Institute of Child Health and Human Development, the University of Virginia Medical Center, Children's Hospital of the University of Pennsylvania, and the Salk Institute collaborated in the study which involved administration of synthetic GRF to 12 adult volunteers with growth hormone deficiency. They found that several of the volunteers responded by making increased amounts of growth hormone, and most produced increased amounts of somatomedin C, the intermediary substance through which growth hormone acts. (The researchers were not looking for growth in the adult volunteers, since further linear growth is impossible once puberty is completed.) These findings suggest that treatment with synthetic GRF during childhood might stimulate growth in some patients with growth hormone deficiency.

GRF can only be used in children, however, once safety and effectiveness has been proven in adults.

Patients involved in this study were hospitalized in General Clinical Research Centers funded by the Division of Research Resources.

Results of the study were published in the July 16 issue of *Lancet*.

- Scientists at the University of Texas Health Science Center at San Antonio have developed an immunotherapy treatment for patients with superficial cancer of the bladder that reduces the incidence of tumor recurrence up to four times more effectively than other therapies. This is a particularly important finding because tumors recur after surgery in 75 percent of the 35,000 patients who develop bladder cancer each year.

Working under a grant from the National Cancer Institute (NCI), the researchers have found that immunotherapy with Bacillus Calmette-Guerin (BCG) vaccine, a type of tuberculosis bacterium, can substantially minimize the bladder tumor recurrence rate by stimulating the body's natural immune system, according to the investigator. Since this stimulation is a short-term effect, however, initial treatment was followed by maintenance BCG immunotherapy. Extended BCG administration resulted in continued protection against tumor recurrence.

Reaction to PPD (purified protein derivative) skin sensitivity testing appears indicative of how well a patient will respond to BCG therapy. Patients who converted from a negative to a positive PPD test had the lowest tumor recurrence rate of five percent, while those whose PPD test remained negative had the highest rate of recurrence (38 percent).

The researchers therefore feel that the correlation between skin test conversion to positive and a reduced incidence of tumor recurrence warrant continued BCG therapy until conversion occurs.

Based on their findings with 185 patients, the researchers believe that maintenance BCG immunotherapy may be beneficial for patients with recurrent bladder tumors.

- The National Cancer Institute (NCI) has initiated a program to investigate biological response modifiers—substances that boost, direct or restore normal defenses of the body—and their effects as potential anticancer agents.

Some of these substances occur naturally in the body (although only in small amounts and for a few hours); others can be manmade. New techniques such as gene-splicing enable scientists to make biological response modifiers in sufficient quantities to study.

Investigators are conducting clinical trials of four groups of these substances: interferons, thymosins, chemical immunomodulators, and monoclonal antibodies.

According to Dr. Kenneth Foon of NCI's Clinical Investigations Section, several Phase I studies have been conducted with both nonrecombinant, or natural interferon and interferon developed by recombinant DNA techniques. The Phase I studies are designed to determine the maximum safe dose level for a new biological substance, the dose at which the maximum biological effect occurs, and the best schedule of administration. The biologics are selected for clinical testing on the basis of highest probability of producing an anticancer effect. Patients are carefully monitored for anticancer effect and toxicity during the course of a Phase I trial. Phase I trial results are then used to select several appropriate doses for Phase II studies. Phase II trials at NCI with recombinant interferon have demonstrated responses in over 50 percent of patients with lymphomas.

Phase I trials with T-101 monoclonal antibodies in chronic lymphocytic leukemia and cutaneous T-cell lymphomas showed a brief reduction in circulating leukemia cells and excellent T-101 antibody localization in tumors cells in the bone marrow, skin, lesions and lymph nodes.

Phase I trials were also conducted with anti-melanoma monoclonal antibodies on ten patients. No clinical response was achieved, however, excellent antibody localization was demonstrated in melanoma tumors in the skin. There were very minor side effects except for two patients who developed serum sickness—the first incidence of this syndrome with monoclonal antibody treatment. This side effect was successfully treated with steroids.

Future monoclonal antibody trials will include various drugs, radionuclides and toxins conjugated to the T-101 and anti-melanoma antibodies. In addition, scientists at NCI are developing special "tailor-made" antibodies for patients with lymphoma termed antiidiotype antibodies. In studies at Stanford University, these antibodies appear to have a very potent antitumor effect.

NCI scientists hope that biological response modifiers will help to improve available treatment for cancer patients.

- Researchers at the University of Florida are making progress towards understanding the hot flashes suffered by women during menopause, through the development of an animal model.

Scientists have found that when rats are addicted to morphine and then withdrawn abruptly from the drug, they show physiological traits like those of women experiencing hot flashes. This development of an animal model will allow testing of various medications for alleviation of the symptoms.

Under a grant from NICHD, researchers hope to localize the brain region involved in producing hot flashes. This symptom is estimated to affect about 75 percent of all women as they go through menopause.

Editors of publications may request a glossy print of the numbered photographs appearing in this issue.

Ms. Maureen Napper
National Institutes of Health
Building 31, Rm. 2B-10
Bethesda, Maryland 20205

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News&Features from NIH

November 1983

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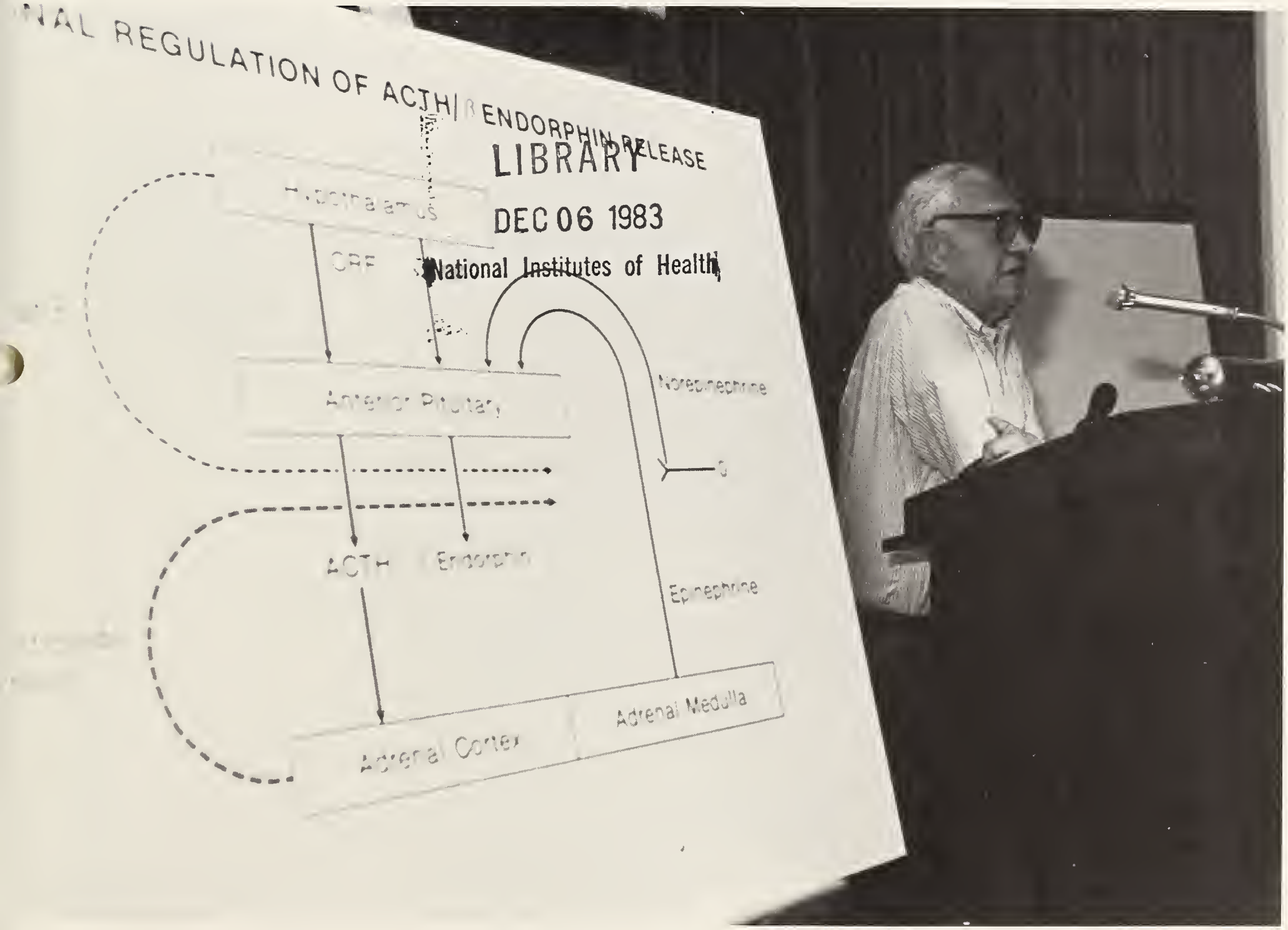
Possible Association Investigated between Pest Control Work and Lung Cancer **p. 7**

Vidarabine Offers New Hope For Shingles Patients **p. 2**



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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

News&Features
from NIH

November 1983

Last year, the National Eye Institute hosted a meeting on eye epidemiology, a field only 10 years old, but rapidly gaining interest among ophthalmologists, statisticians, and other vision researchers.

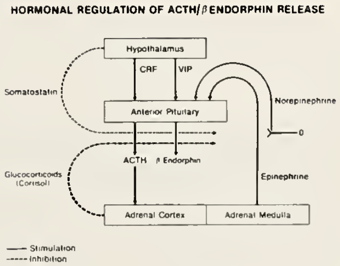
With NEI support, clinical trials and epidemiology studies have provided on-the-job training and prompted ophthalmology departments to add epidemiologists and biostatisticians to their staffs.

Presentations from the symposium on the epidemiology of many chronic eye disorders including cataract, senile macular degeneration, diabetic retinopathy and glaucoma were published recently. See page 9

NICHD wishes to correct a false impression given by a headline written by News and Features staff for the story on IUDs and breastfeeding in the August issue. The researchers did not warn women not to use IUDs when breastfeeding. They did, however, warn clinicians to exercise caution when inserting IUDs in breastfeeding women.

Severe stress early in life can result in permanent hyperreactivity to stressful situations later, according to NIH and National Institute of Mental Health scientists.

Researchers at an NIH Science Writers' Seminar held recently discussed studies showing how the body's stress response is mediated through the hypothalamic-pituitary-adrenal (HPA) axis. See page 4


HORMONAL REGULATION OF ACTH/β ENDORPHIN RELEASE

NIH Photo 1913

The level of glucose metabolism in the brain seems higher in young adults with Down's syndrome than in normal subjects, according to a recent NIH study.

A collaborative effort by NIH researchers has noted that mental retardation, a characteristic of Down's syndrome, may be associated with this altered metabolism in the brain. See page 2

Vidarabine can effectively treat the sometimes fatal complications of herpes zoster in immunocompromised patients, as shown by studies supported in part by the National Institute of Allergy and Infectious Diseases.

Herpes zoster is not usually a life-threatening condition, but in some cases it is fatal if the virus spreads to vital organs in these patients.

Until now there has been no effective treatment. See page 2

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Editorial Staff

Susan Gerhold
Acting Editor

Sandra D. Levine
Assistant Editor

Maureen Napper
Editorial Assistant

NIH News Branch
Building 31, Room 2B-10
Bethesda, Maryland 20205

hone:
01) 496-2535

Vidarabine Shows Promise in Treatment of Patients with Shingles

Patricia Randall

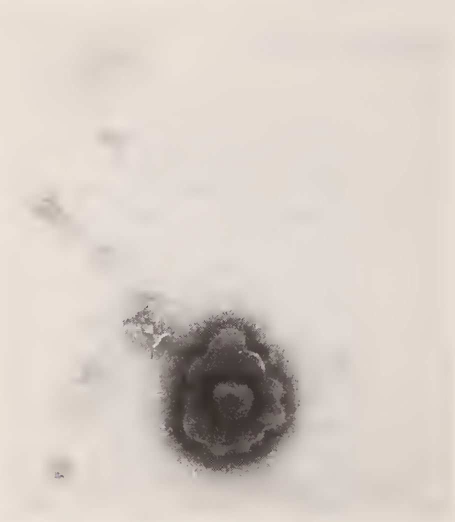
Vidarabine, a drug used to treat patients with herpes virus encephalitis, can also prevent life-threatening complications of herpes zoster (shingles) in immunocompromised patients, according to studies supported by the National Institute of Allergy and Infectious Diseases (NIAID). The Food and Drug Administration (FDA) recently approved this new use of the drug.

Although the number of patients who may benefit from this treatment is small, Dr. Richard M. Krause, NIAID director, emphasizes the importance of vidarabine as a life-saving drug and as a pioneer product in the long search for drugs effective against viral infections.

Earlier NIAID-supported studies led to initial approval of vidarabine as the first injectable drug for treatment of patients with a serious viral infection.

Herpes zoster is caused by reactivation of the chickenpox virus, occurring in 10 percent of the population, usually after age 50. It produces a blistery rash on the skin and pain that sometimes persists for several weeks after the lesions have healed (postherpetic neuralgia). Although uncomfortable, herpes zoster is not life-threatening for most people.

However, in persons whose immune systems are affected by underlying disease or by treatment with anticancer drugs, herpes zoster can spread from the skin to vital organs of the body and may cause death. Until now, there has been no effective treatment for the disease.



The culprit: Shingles and chickenpox are caused by the same virus, isolated here from laboratory studies. The central core of the virus is about 5 millionths of an inch across.
NIH Photo 1914

In the NIAID-supported study, physicians administered either vidarabine or a placebo to immunocompromised patients within 72 hours after they developed herpes zoster. The drug or placebo was given intravenously over a 12-hour period on 5 consecutive days.

Neither patients nor physicians knew which substance was being given. Only 5 percent of 63 vidarabine-treated patients with herpes skin lesions developed zoster-related systemic complications compared to 19 percent of the 58 placebo-treated patients.

Vidarabine accelerated healing of the skin lesions and decreased the frequency of lesion spread to other skin areas. Lesion spread occurred in 24 percent of untreated patients but in only 8 percent of treated patients. Treatment also reduced the length of time patients suffered postherpetic neuralgia.

Four months after the onset of the infection, 56 percent of the treated patients were free of pain compared to only 17 percent of untreated patients.

Physicians noted that patients with lympho-proliferative cancers and those 38 years of age or older were at greatest risk for complications of herpes zoster, and they benefited most from therapy. None of the patients suffered serious side effects.

This study, the Collaborative Antiviral Study Group, was done as part of an ongoing NIAID-sponsored program to test antiviral substances at collaborating medical research centers throughout the country.

The research was reported in the *New England Journal of Medicine*. The study was supported by a contract from NIAID, by grants from the National Cancer Institute and from the NIH Division of Research Resources' General Clinical Research Centers Program, and by the Robert Meyer Foundation. ■

Photo courtesy of:
Dr. William T. Ruyechan
Uniformed Services University of the Health Sciences
National Naval Medical Center
Bethesda, Maryland

Brain Metabolism in Down's Patients Studied by Several NIH Components

Marian Emr/David Moore

A collaborative NIH study has recently found that brain glucose utilization is elevated by 30 to 40 percent in young adults with Down's syndrome. Down's syndrome is the most common form of mental retardation with a known cause. Down's patients have an extra 21st chromosome, and some Down's patients older than age 35 frequently show the mental symptoms of Alzheimer's disease. Results of this study, conducted by the National Institute on Aging (NIA), the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), and the Clinical Center's Nuclear Medicine Department, were reported in the August 19 issue of *Science*.

Dr. Stanley Rapoport, chief of the Laboratory of Neurosciences, NIA, led a research team which measured brain metabolism in four Down's patients younger than 35 years of age, in one 51-year-old patient, and in healthy age-matched volunteers. Measurements were performed under resting conditions by means of positron emission tomography (PET), a technique used to study brain function.

PET uses a chemical analogue similar in structure to glucose to monitor metabolic activity in different regions of the brain. Glucose, or sugar, is the main source of the brain's energy. A radioactive positron-emitting label on the chemical allows specific areas of the brain to be visualized by computerized image-processing.

The current study measured glucose metabolism in the cerebral hemispheres, the upper portion of the brain which is responsible for thought processes, organized motor behavior, sensation, speech and hearing.

The results revealed a higher level of glucose metabolism in the brains of the four younger Down's patients (ages 19 to 27) than in healthy subjects of the same age. These results indicate that glucose is used excessively by brains of young adult Down's patients, and that the mental retardation of Down's syndrome may be associated with a metabolic alteration in the brain.

The investigators also looked at a 51-year-old Down's patient and found that glucose utilization was lower than in the younger Down's patients. In another Laboratory of Neurosciences study (in press, *Brain*) shows no age-related decline in brain metabolism in healthy individuals. Taken together, these findings suggest that brain activity declines as Down's patients age. The findings are also consistent with recent evidence that brains from many older Down's patients exhibit the nerve cell degeneration and reduced activity of enzymes that characterize Alzheimer's disease.

Although the NIA scientists are cautious about drawing conclusions from their results, their findings clearly indicate that PET can be employed to examine brain function in Down's syndrome and other diseases. ■

New Cell Separation Technique in Space May Lead to Improved Treatment of Diabetes

Charlotte Armstrong

Researchers are busy looking over a cargo of pancreas cells that the NASA space shuttle Challenger carried with it on its August flight. The information that the scientists will gather over the next few weeks may help them in developing a new means of treating diabetes.

The cells were from the laboratory of Drs. Paul Lacy and David Scharp, researchers at the Washington University School of Medicine in St. Louis. Supported by a grant from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), the experiment tested, in an environment with no gravity, a cell separation technique developed by McDonnell Douglas Corporation. The researchers are hoping that separating cells by this technique might provide larger and more concentrated yields of cells that are suitable for transplantation than can be obtained on the Earth's surface.

The Washington University researchers will not know what kind of yield they have for several weeks. However, the returned cells are alive, and migration patterns of the cells in the apparatus used to separate them in space are similar to those observed on the ground.

Successful transplantation of the insulin-producing beta cells, or of the whole pancreas, has been the object of a considerable amount of research over the years. In normal individuals, the pancreas, a gland just below the stomach, produces the hormone insulin, which is essential for glucose in the blood to be metabolized for energy. In people with the insulin-dependent form of diabetes, the pancreas secretes little or no insulin, and daily injections of insulin and a controlled diet are necessary for survival.

Drs. Lacy and Scharp's approach to transplantation of pancreas tissue has been to isolate and transplant only those cells of the pancreas that secrete insulin in the hope that this would minimize or eliminate the possibility of rejection of the transplanted tissue by the recipient's body.

In research over the years, the scientists have developed means of separating these insulin-secreting or beta cells from the pancreas and then transplanting them into an animal with no functioning pancreas. One hurdle in the success of this technique has been to harvest enough beta cells from one donor to provide the recipient with all of its insulin needs.

Drs. Lacy and Scharp collaborated with McDonnell Douglas Corporation and NASA in order to test the new separation technique, which uses continuous flow electrophoresis. The device continuously injects a stream of the biological materials to be separated into a buffer solution flowing through a thin, rectangular chamber. An electrical field applied to the chamber causes the biological materials to separate on the basis of differences in size and electrical charge.

The technique can be used on the ground, but gravity exerts its own force on the subject materials, interfering with even separation. In previous tests in space, the device has shown the ability to separate over 700 times more materials and to achieve purity levels more than four times greater than is possible in similar operations on Earth.

The cells carried on the space shuttle will be used only for *in vitro* studies as opposed to tests in living animals. If results from this first trial are positive, Dr. Scharp expects that the process will be repeated in the future, providing additional cells for testing.

Testing new techniques of isolating insulin-producing beta cells is only one aspect of the research needed before beta cell transplantation in human beings with diabetes can be attempted. Cell culture methods are being tested and research on pancreas tissue transplantation is being conducted in animals in order to clarify the mechanism of rejection of donor tissue and which kinds of transplanted tissue cause rejection; to determine how long transplanted islet cells will function in the recipient and how many cells are needed to provide the recipient with adequate control of a diabetic condition; to identify where the transplanted cells will function best in the recipient; and to determine whether islet cells can be transplanted successfully from one species to another.

The development of a successful means of pancreatic islet transplantation could conceivably provide sufficiently improved management of the metabolic abnormalities in people with the insulin-dependent form of diabetes. Present treatment of diabetes with intermittent doses of insulin does not mimic the natural function of the pancreas, which responds minute to minute to changes in blood glucose level.

Some physicians feel that fluctuations in blood sugar experienced by people taking insulin injections, in addition to causing short-term problems such as episodes of abnormally high or low blood sugar, may also contribute to the development of long-term complications of diabetes such as loss of vision, and nerve and kidney disease. Pancreas transplantation could solve these problems by more closely mimicking the natural action of the pancreas.

While whole pancreas transplantation is now being performed in clinical research studies on selected patients with severe diabetes, the operation does not yet provide complete control of diabetes in a high percentage of pancreas recipients. The partnership of space exploration and medical research may have the unexpected payoff of providing a better means of treating people with diabetes. Dr. Scharp said that "preliminary experiments using cells from the pancreas in the McDonnell Douglas electrophoresis device suggest that this technique may bring islet transplantation to the diabetic patient sooner by providing greater quantities of purified beta cells." ■

The Mechanism of Stress is Examined at Science Writers' Seminar

Jules Asher

Psychiatrists have long observed that stress can trigger episodes of depression in susceptible individuals. Now the National Institute of Mental Health (NIMH) and NIH scientists have turned up new biological clues as to how a key brain hormone may become hyperreactive in affective disorders, precipitating a cascade of abnormal endocrine responses typically seen in depressed patients.

The findings suggest a new model for understanding how severe stresses early in life might lead to permanent hyperreactivity to stress and mood disorder in vulnerable persons.

Drs. Philip Gold of NIMH and George Chrousos of the National Institute of Child Health and Human Development (NICHD) discussed such possible implications of their experiments with the recently purified neurohormone corticotropin releasing factor (CRF), at an NIH Science Writers' Seminar on the "Molecular Basis of Stress" in July.

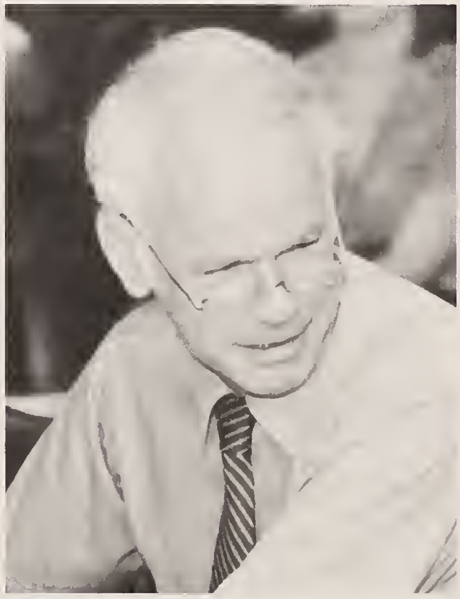
The seminar, moderated by Dr. Frederick Goodwin, director of the NIMH Intramural Research Program, also featured presentations by Drs. Julius Axelrod and Steven Paul, both of NIMH.

Much of the discussion centered on new findings about how the body's stress response is mediated via the hypothalamic-pituitary-adrenal (HPA) axis. Although a more complex picture emerged at the seminar, this biological pathway basically represents a classic negative feedback system: In response to a stressor, the brain's hypothalamus secretes CRF, which stimulates the pituitary gland (located just beneath the brain) to release the hormone ACTH into the bloodstream. This hormone in turn causes the adrenal glands (located on top of each kidney) to secrete cortisol. In the bloodstream cortisol triggers a variety of responses, readying the organism to deal with the demanding situation. Cortisol also inhibits ACTH release from the pituitary, thereby controlling its own levels.

The availability of synthetic CRF within the past year has spurred a new wave of studies on the HPA axis. Drs. Gold and Chrousos reported on the first experiments using the hormone as a challenge drug in primates and humans.

When injected with CRF, depressed patients showed a lower response in their blood ACTH levels than did controls. This blunted response is likely due to the fact that depressed patients commonly have abnormally elevated levels of cortisol in their blood. Hence, this finding suggests that the feedback regulation of ACTH release by cortisol at the pituitary remains unimpaired in depression—i.e., that depression is a problem of the hypothalamus and/or higher brain centers.

Dr. George Chrousos of NICHD (left), and NIMH's Dr. Philip Gold (right), collaborated on studies on the role of CFR in patients with depression, Cushing's syndrome, and Addison's disease. NIH Photo 1915


The seminar was moderated by Dr. Frederick Goodwin, director of the NIMH Intramural Research Program. NIH Photo 1916

Dr. Steven Paul presents his research on the benzodiazepine receptor complex. NIH Photo 1917

When normal subjects received a continuous infusion of CRF, their blood cortisol levels showed a modest rise that mimicked the cortisol levels of many depressed patients. The scientists also reported that growth hormone levels of depressed patients injected with CRF resembled those of similarly stimulated stressed primates; both were elevated. These findings suggest that depression involves an excess of CRF secretion, according to Drs. Gold and Chrousos.

The CRF stimulation test they developed also enabled the scientists to differentiate depression from Cushing's disease, another disorder of the HPA axis characterized by elevated cortisol levels and secondary depressions along w[illegible] such symptoms as obesity, high blood pressure, and weak bones and connect-

Dr. Julius Axelrod explains his findings on the relationship among the stress hormones—catecholamines, ACTH, and glucocorticoids. NIH Photo 1918

ive tissue. Some investigators had proposed that depression and Cushing's disease might stem from the same source. However, Cushing's patients' ACTH levels soared following CRF injections, indicating failure of the pituitary to cease ACTH secretion despite high levels of blood cortisol. This localizes Cushing's disease as a problem of the pituitary, said the researchers.

Building on these and other findings, Dr. Gold offered what he cautioned was simply a theory that early prolonged stresses might sensitize genetically vulnerable individuals to chronically oversecrete CRF and hyperreact to stress later in life. Among the points offered as supporting evidence were the following: A tendency for depressed patients to have a history of early stresses (particularly separations) associated with intense anxiety and to relive repetitively these feelings during stressful times is a common theme in clinical psychiatric literature. Animal studies have found permanent rises in the reactivity of HPA axis hormones in response to stresses administered during early critical periods. CRF is known to activate the locus ceruleus, an anxiety-mediating center of the brain; intense anxiety is a common feature of depression. When injected in animals, CRF can also induce limbic seizures and associated freeze postures, phenomena seen in some depressed patients; antidepressant drugs act as limbic anticonvulsants.

Since HPA activation and depressive symptomatology are not unique to primary depression, excessive CRF secretion may also figure in other psychiatric illness such as anorexia nervosa and obsessive-compulsive disorder, Dr. Gold suggested. He added that CRF may also play a broader role in orchestrating the stress response through activity in parts of the brain other than the hypothalamus.

According to Dr. Goodwin, such findings as excess CRF need not prove to be the "single defect" in depression to influence diagnosis and treatment. "Many treatments in medicine work on pathophysiological chains considerably downstream from a postulated ultimate cause," he said, noting that opportunities for "breaking the chain" of dysfunctional stress responses through pharmacological intervention may emerge from the kind of work reported on at the seminar.

While a modicum of stress is actually essential to health and normal adaptation, depressed patients often seem as if they are in the throes of a hyperstressful situation, explained Dr. Goodwin. There is now evidence that antidepressant drugs may, in effect, serve as "stress substitutes" for such vulnerable individuals, perturbing the brain and strengthening its ability to adapt. Studies are showing that like chronic stress, antidepressants increase the capacity of the brain's catecholamine (epinephrine/norepinephrine) system to respond.

In studies designed to understand how this key system interacts with the other hormones of the HPA axis, NIMH neurochemist and Nobel laureate Dr. Julius Axelrod discovered that the regulation of the stress response is more complex than had been thought. He described how he circumvented the pituitary gland's complexity by performing his experiments in a simple, accessible type of cell, the AtT-20, a mouse pituitary tumor cell line. Unlike normal pituitary cells, the AtT-20 secretes only two substances, ACTH and the natural opiate beta-endorphin, and can be easily cultured. Dr. Axelrod then confirmed his discoveries in the functioning pituitary in rats.

He found that, like CRF, catecholamines from the cortex and adrenals stimulate the pituitary to release ACTH. Catecholamines bind to beta 2-adrenergic receptors on the pituitary cell membranes and stimulate a "second messenger" substance within the cell called cyclic AMP, which in turn signals the cell to synthesize and release its hormones. He also discovered that another brain substance called vasoactive intestinal peptide (VIP) acts similarly on the pituitary to stimulate release of ACTH. Another hormone, somatostatin, has just the opposite effect, shutting off cyclic AMP and blocking ACTH secretion. Levels of ACTH were found to decrease when the pituitary was chronically stimulated, suggesting sensitization or "down-regulation" of the system under chronic stress.

"These findings reveal a sophisticated system by which the organism at once maintains a vital homeostasis while coping with a challenging environment," observed Dr. Axelrod, who has now embarked on experiments to determine which hormone systems are differentially activated by different types of stressors. "Vulnerability to stress-related illness seems to stem from a breakdown in the fine-tuning of this intricate system," he added.

Moving "upstream" from the HPA axis to the cortical areas of the brain, NIMH psychiatrist Dr. Steven Paul reviewed experiments localizing the mediation of a major form of stress—anxiety—to the benzodiazepine (Valium) receptor complex. Not only does the benzodiazepine receptor respond to drugs that reduce anxiety but it can also recognize drugs which produce anxiety in monkeys and humans.

In what Dr. Paul described as a "rather surprising" series of experiments, he found that a beta carboline substance (β-CCE) triggered behavioral and physiological effects closely resembling anxiety in rhesus monkeys. After β-CCE injections, the β-CCE injections, the animals became aroused and agitated and showed elevated heart rate, blood pressure, and catecholamine, ACTH, and cortisol levels. All of these effects of β-CCE were blocked by pretreatment with benzodiazepines, confirming that they were mediated via the benzodiazepine receptor.

In experiments by German investigators, administration of a chemical cousin of β-CCE produced an emotional experience indistinguishable from anxiety in human volunteers, again accompanied by the same somatic and endocrine changes observed in Dr. Paul's monkeys.

He is now initiating studies to determine whether patients with anxiety disorder have any abnormalities in their benzodiazepine receptor complex. In addition to the benzodiazepine recognition protein itself, Dr. Paul and colleagues have found that this complex also consists of related receptors for the inhibitory neurotransmitter GABA and a chloride ionophore—a channel that regulates the flux through the cell membrane of the chloride ions, which control the nerve cells' firing rate. ■

Two Recently Tested Anti-Inflammatory Drugs Seem to Alleviate Pain in the Removal of Wisdom Teeth

Jody Dove

Patients given either ibuprofen or flurbiprofen—two nonsteroidal anti-inflammatory drugs—before undergoing removal of impacted third molars report significantly less postoperative pain than patients receiving more commonly used analgesics.

This important finding emerged from studies conducted by the National Institute of Dental Research's (NIDR), Raymond A. Dionne, D.D.S., Ph.D., and colleagues who tested the hypothesis that it is possible to suppress postoperative pain by preoperatively administering drugs capable of inhibiting the inflammatory response normally observed following surgical procedures such as the removal of third molars. Ibuprofen, more commonly known as Motrin or Rufen, has been used for the relief of mild to moderate pain and in the treatment of rheumatoid arthritis. Flurbiprofen is an investigational new drug that is structurally similar to ibuprofen and is also well-tolerated. This drug was chosen for the second study because previous reports had indicated that it might even be more potent than ibuprofen. Both drugs are believed to be effective because they suppress the release of prostaglandins which are responsible for mediating pain and inflammation.

The NIDR study was conducted in conjunction with researchers at the Medical College of Virginia and the University of Medicine and Dentistry of New Jersey. One hundred and seven dental outpatients undergoing surgical removal of impacted third molars were randomly assigned to one of four treatment groups: placebo, ibuprofen, acetaminophen, or acetaminophen plus codeine.

In this double-blind clinical trial, patients received local anesthesia and diazepam sedation prior to the surgery, in addition to the drug dose of their particular treatment group. Subjects received a postoperative dose of pain medication four hours following the initial dose and were retained at the clinic up to eight hours.

Data in pain intensity following the first two drug doses were collected hourly by a research nurse. Patients rated their pain as "none," "slight," "moderate," or "severe," and also reported any side effects.

Results from the study indicate that ibuprofen significantly lessened pain in comparison to placebo, pretreatment with acetaminophen, or postoperative administration of acetaminophen plus codeine.

The flurbiprofen study consisted of a within-subject, crossover design involving three groups of 20 patients. The upper and lower third molars on one side were removed at the first appointment, and the molars on the other side of the mouth were extracted at the second appointment. The first group of patients received either flurbiprofen or acetaminophen pre- and postoperatively for the first set of extractions and the alternative treatment for their second set of extractions two weeks later. A second group of patients received either flurbiprofen pre- and postoperatively or acetaminophen plus oxycodone (more commonly known as Percocet) postoperatively. The third group received either flurbiprofen or acetaminophen plus oxycodone both pre- and postoperatively.

All patients were given diazepam and a local anesthetic prior to surgery. Half of the subjects received the standard drug at the first appointment and the experimental drug at the second appointment, while the order was reversed for the other half of the subjects.

Hourly observations of analgesic effects were made from two to eight hours after the first drug dose was administered. Pain was classified according to the same scale used in the ibuprofen study. A visual analog scale and two other experimental measures were also employed, and subjects were questioned about side effects.

In all three phases of the study, patients reported significantly less postoperative pain with flubiprofen and expressed a clear preference for this drug.

Pretreatment with flurbiprofen was superior to the maximum dose of acetaminophen that is routinely employed. Moreover, a comparison of pretreatment with flurbiprofen to the standard treatment of postoperative administration of acetaminophen plus oxycodone also demonstrated the superiority of this anti-inflammatory agent. Even preoperative administration of acetaminophen plus oxycodone did not suppress postoperative pain nearly as well as flurbiprofen.

Side effects reported by patients in both the ibuprofen and flurbiprofen studies were mild and consisted of headache, drowsiness, dizziness, and gastrointestinal upset. There were no differences among the treatment groups, except that more patients reported drowsiness in the acetaminophen-opiate groups.

The removal of impacted third molars is an excellent dental pain model for evaluating the effectiveness of analgesics because 95 percent of patients report moderate to severe pain within four hours after surgery. In the NIDR studies, the highest mean pain rating of ibuprofen and flurbiprofen was equivalent to mild pain. These studies suggest that analgesic drugs that inhibit prostaglandin synthesis are more effective in suppressing postoperative pain than drugs that do not interfere with this pathway. Ibuprofen and flurbiprofen both delay the onset and suppress the intensity of postoperative pain to a greater extent than traditional oral analgesic therapy without an increase in side effects. ■

Possible Association Found Between Pest Control Work and Lung Cancer

Linda Anderson

Structural pest control workers may be at increased risk for lung cancer from chemical exposures, suggests a new study by National Cancer Institute (NCI) scientists. The findings appear in the July issue of the *Journal of the National Cancer Institute*.

The kinds of structural pest control work in the study included extermination of termites and other wood-infesting organisms, general household pests, rodents, and lawn and ornamental shrub pests, and fumigation work. Risk for lung cancer could be evaluated separately only for lawn and ornamental shrub pest control workers, and no excess lung cancer risk was found among workers whose firms were licensed only for this purpose. Risk for lung cancer could not be attributed to specific pesticides because of lack of information on types and amounts of exposure.

According to the findings, the risk for lung cancer increased with length of employment, which suggests that close and prolonged exposure to pesticides may contribute to risk for the cancer. Information on cigarette smoking was not available. However, according to the scientists, it is unlikely that smoking would account entirely for the excess deaths from lung cancer.

The scientists also found that the excess risk was greater among men who were first licensed as structural pesticide applicators before age 40. This may have been due to more intensive exposure, they speculated, if these younger men had held entry-level jobs with duties that involved heavier exposures. The study did not gather this type of detailed information, however.

The findings do not prove a causal relationship between pesticides and lung cancer. Other occupational studies also have suggested that pesticides may be risk factors for lung cancer, and some pesticides that are used in this occupation are known animal carcinogens. Thus, these new findings point out the need for further epidemiologic study to clarify the potential carcinogenic risk of pesticides.

The principal pesticides used by structural pesticide workers during the 1950s and 1960s were organochlorine chemicals. These include chlordane, heptachlor, dieldrin, DDT, lindane, and toxaphene, which are all recognized as animal carcinogens by the International Agency for Research on Cancer (IARC). These chemicals were gradually replaced in the 1960s and early 1970s by organophosphates such as malathion, diazinon, and dichlorvos or by carbamates such as propoxur and carbaryl. Of these examples, carbaryl is recognized by IARC as an animal carcinogen. Most workers studied could have had contact with any or all of these pesticides.

The scientists evaluated deaths that occurred among 3,827 white men who were licensed as structural pest control workers in Florida in 1965 and 1966. Florida requires pest control firms to renew their licenses annually and list the names of employees who perform the work. Data on deaths among these workers were collected through 1976, and were compared with deaths among the United States population for white men of the same age. The number of nonwhite men was not large enough to include in the analysis.

There were 34 deaths from lung cancer among the pest control workers over the 12-year period from 1965 to 1976, compared with 25.1 that would be expected in the general population.

The risk increased with the amount of years the workers were licensed: 15 deaths among men who were licensed less than 10 years, compared with 14.8 deaths that would be expected; 11 deaths among men licensed from 10 to 19 years, compared with an expected 7.1 deaths; and 8 deaths among men licensed 20 years or longer, compared with an expected 2.8 deaths.

Among workers who were first licensed before age 40, there were 11 lung cancer deaths, which was more than double the expected number of 4.7 deaths. Among those first licensed after age 40, there were 23.0 deaths, compared with an expected 20.0 deaths.

The reason that no excess lung cancer risk was found for workers whose firms were licensed only for lawn and ornamental shrub pest control is not understood, because these workers were exposed to many of the same pesticides as the other pest control workers. Perhaps these workers had less intense exposures because they worked outdoors, in less confined spaces than other kinds of pesticide applicators, the scientists said. There were 7 deaths from lung cancer among the workers while 7.6 would be expected.

The scientists believe that smoking would not account entirely for the excess deaths from lung cancer for a number of reasons. For example, they found no overall pattern of excess deaths from smoking-related disorders among the workers, and death rates were lower than would be expected for some, including cardiovascular disease and esophageal cancer. Even if 80 percent of the workers who were licensed 20 years or more had smoked, the scientists said, an estimated 65 percent excess of lung cancer deaths would be expected. In the study, however, there was nearly a three-fold (289 percent) increased risk among the workers.

The lawn and ornamental shrub pest control workers were the only group exposed to herbicides. No excess deaths from lymphomas and soft-tissue sarcomas were found among the workers. This is noteworthy because other studies have found apparent increases in risk for these cancers associated with herbicide exposure.

The scientists also observed slight excesses of deaths from leukemia and brain cancers, although the number of deaths was not statistically significant and could be explained by chance. There were 3 deaths from acute myelocytic leukemia among the workers, compared with 0.9 that would be expected. This finding is of interest because this type of leukemia has been associated with chemical exposures in other studies. There were 5 deaths from brain cancer, and 2.5 deaths would be expected.

Overall, the mortality experience for all cancers was only slightly higher for the workers than for the general white male population, and this difference may have been due to chance. There were 84 cancer deaths among the workers, and 73.7 deaths would be expected.

Further research will be necessary to determine whether pesticide exposures received in this type of work increase the risk of lung cancer. ■

Researchers Find that AIDS Patients Have Defects in T and B Cells

Patricia Randall

A team of scientists, headed by Dr. Anthony S. Fauci, of the National Institute of Allergy and Infectious Diseases (NIAID), has found that patients with Acquired Immune Deficiency Syndrome (AIDS) have functional defects in both major classes of lymphocytes, both T cells and B cells, that usually protect the body against disease.

Until now, investigators believed that the immune abnormalities in AIDS patients involved only the T cells, specifically a decrease in the helper/inducer subset of T cells. Among other functions, the helper/inducer cells normally work with the suppressor subset of T cells to regulate antibody production by B cells.

Dr. Fauci and his colleagues studied 12 homosexual men with AIDS, 5 healthy homosexual men, and 12 heterosexual controls. As expected, the AIDS patients were deficient in helper/inducer T cells and had decreased helper-to-suppressor T-cell ratios. In addition, when the subsets of T cells were studied separately in the laboratory, the scientists found that, although the suppressor cells functioned normally, the helper cells did not.

Further studies showed marked abnormalities in B-cell activation and regulation in the patients. Their B cells did not react to substances that ordinarily stimulate antibody production. Also, the patients had abnormally high numbers of B cells spontaneously secreting different kinds of antibodies (polyclonal activation).

This increase in activated B cells is similar to what occurs during certain viral infections, such as mononucleosis. In that case, the Epstein-Barr virus infects the B cell, which becomes transformed and begins spontaneously to secrete antibody. Infections with cytomegalovirus cause similar reactions.

Generally, after such infections, T-cell regulators step in to restore normal balance to the immune system. In the case of the AIDS patient, the defective helper/inducer T cells may fail to stimulate the suppressor cells to slow the abnormal B-cell activity.

The healthy homosexual men in this study also showed alterations in immune function when compared to the heterosexual control group. Although there were wide variations in the immune responses of the healthy homosexuals, the results generally fell between those of the AIDS patients and the heterosexual controls. What causes these alterations and how they relate to AIDS is still unknown.

Dr. Fauci stresses that the cause of AIDS remains a mystery. This study reveals B-cell abnormalities that are highly suggestive of viral stimulation in the absence of normal regulatory T-cell activity. More research is needed on the B-cell defects as well as on the T-cell dysfunction in AIDS patients.

This study was reported in the August 25 issue of the *New England Journal of Medicine*. ■

Growth Factor, Simian Virus: Common Clues to Cancer

Florence Karlsberg

Protein produced by a gene responsible for the cancer-causing activity of a monkey virus has been found to be strikingly similar to a wound-healing protein found in human blood cells known as platelets, a team of scientists has reported.

Called platelet-derived growth factor (PDGF), the blood protein triggers the process of healing after injury by stimulating cells around the wound site to begin multiplying. This research was reported in the July 15 issue of *Science*.

"The finding may help us understand how cancer genes transform normal cells into rapidly dividing cancer cells with uncontrolled growth," said one of the authors, Dr. Stuart A. Aaronson, National Cancer Institute (NCI).

The researchers suggested that this cancer gene, v-*sis*, may either produce an altered protein product after damage to its DNA, or "turn on" production of this protein in a cell where it is not normally made.

In either case, the cell somehow responds inappropriately by continuing to grow in the uncontrolled fashion typical of cancer.

The partial amino acid sequence of PDGF was described in the May 27 issue of *Science* by Dr. Michael Hunkapiller, California Institute of Technology, Pasadena, and Dr. Harry Antoniades, Center for Blood Research and the Harvard University School of Public Health.

Dr. Russell R. Doolittle, University of California, San Diego, has been storing the amino acid sequences of proteins in a computer bank for his studies of protein evolution. When he entered the amino acid sequence of PDGF into this data bank, he discovered that 87 percent of the 70 amino acids in the known segments of PDGF matched those in the sequence of amino acids of the v-*sis* protein.

The v-*sis* gene and its protein product were discovered, sequenced, and studied in detail by Dr. Sushilkumar G. De Vare, Dr. Keith C. Robbins, and Dr. Aaronson and colleagues in the NCI Laboratory of Cellular and Molecular Biology.

"Considering the species differences," said Dr. Aaronson, "we would expect a 13 percent mismatch between human and monkey proteins with the same functions."

It is too early to assess the clinical importance of these findings," he said. "It is possible, however, that once the protein products of cancer genes are identified and scientists determine how they function, steps can be taken to alter cancer progression by interfering with or inhibiting the biologic activity of those proteins," Dr. Aaronson added.

The scientists are planning future collaborative research to determine whether the function of the monkey protein made by the v-*sis* cancer gene is identical to the human PDGF, and whether other cancer gene proteins may be matched with other normal growth proteins. ■

Results of NEI-Sponsored Epidemiology Meeting Published

Claudia Feldman

Interest in eye epidemiology, a field in its infancy only 10 years ago, drew 130 epidemiologists, ophthalmologists, statisticians, and other vision researchers to the National Institutes of Health last year for the first symposium of its kind in the United States. Selected presentations from this meeting were published in the August issue of the *American Journal of Epidemiology*.

In his opening address at the symposium, Fred Ederer, chief of the National Eye Institute's (NEI) Office of Biometry and Epidemiology (OBE), remarked on the growing interest in eye epidemiology and traced factors contributing to the increase in the number of scientists working in this specialty.

NEI support of randomized clinical trials and other epidemiologic studies has provided on-the-job training in epidemiologic principles and methods.

It has also spurred departments of ophthalmology to add biostatisticians and epidemiologists to their staffs, and epidemiology departments to include staff members with a major interest in eye disease, he said.

In addition, educational activities of the OBE have stimulated interest in eye epidemiology and encouraged researchers to develop the skills needed for such work. OBE educational projects other than the epidemiology symposium have included workshops, publications, annual courses for clinical vision researchers, and an epidemiology fellowship program for ophthalmologists.

The focus of the symposium was on chronic eye diseases and vision disorders occurring in the United States. Critical reviews of the literature on the epidemiology of cataract, senile macular degeneration, diabetic retinopathy, amblyopia, and glaucoma were presented as well as 28 reports on individual research projects. Four of the literature reviews and nine of the reports were presented in this special issue of the *American Journal of Epidemiology*.

In one report, Dr. Lawrence I. Rand at the Joslin Diabetes Center, Boston, discussed his case-control study of insulin-dependent diabetics and presented preliminary results.

The objective of his study is to identify personal, biological, familial, or environmental factors that could explain why some diabetics develop diabetic retinopathy and lose vision while others do not. He is investigating such risk factors for diabetic retinopathy as control of diabetes, blood pressure, smoking, growth hormone levels and HLA antigen types.

A case-control study of risk factors for senile macular degeneration (SMD) was presented by Dr. Leslie Hyman, a researcher at the State University of New York at Stony Brook. Statistically significant associations were found between SMD and a maternal and sibling history of the disease and between SMD and light iris color.

The study suggested that genetic factors were strongly associated with SMD in both men and women, and that exposure to industrial chemicals and cigarette smoking were weakly linked to development of the disease.

Dr. Hyman and her colleagues also looked into risk factors for the neovascular form of SMD, a potentially blinding disease which is characterized by the growth of abnormal new blood vessels in the eye.

They found associations betweeen this more critical form of the disease and increased age and cardiovascular disease. Decreased hand grip strength (an indication of physiological aging) was a significant factor only when cardiovascular disease was present.

Also discussed at the symposium was the Visual Acuity Impairment Survey (VAIS). This study was designed to provide prevalence data on impairment of distance visual acuity and on the diseases which cause it, and study cases of impairment from the major eye diseases: cataract, senile macular degeneration, glaucoma, diabetic retinopathy and amblyopia.

A pilot study was undertaken first to determine the feasibility of conducting the VAIS in 15 to 20 metropolitan areas. In the pilot study, NEI, in collaboration with the National Center for Health Statistics and the Bureau of the Census, gathered data on visual impairment and its causes.

In a summary statement at the end of the meeting, Mr. Ederer said the conference revealed needs for standardized definitions of eye diseases, and more studies to analyze the differences in the prevalence and incidence of eye diseases in different populations.

He also noted the need for more well designed case-control and cohort studies of eye disease in clearly defined populations and studies to evaluate observer error, and technological advances to simplify and increase the reliability of observations by ophthalmologists. ■

MEDICAL CAPSULES

Sandra D. Levine

- The recent finding that some patients with diabetes have unusually high levels of a growth-mediating hormone may help identify those diabetic patients who may be at high risk for rapid deterioration of vision from diabetic retinopathy, a condition in which small blood vessels grow abnormally on the retina.

The study of 80 patients (31 with Type 1 or insulin-dependent diabetes; 49 with Type II or non insulin-requiring diabetes) and 62 controls was reported in the September 1 issue of the *New England Journal of Medicine*.

Seven of the 31 patients in the study with insulin-dependent diabetes had rapidly progressive diabetic retinopathy. The researchers found that the average level of the growth-mediating hormone in these patients was almost twice that in other patients with Type I diabetes. In addition, patients with insulin-dependent diabetes as a group had higher levels of the hormone than either patients with non-insulin dependent diabetes, or people without diabetes. This finding may help identify patients with diabetes who are at high risk for deterioration of vision.

It is also possible, though not proven, that the hormone may have a role in the development of diabetic retinopathy. The hormone, IGF-1, or insulin-like growth factor, is so named because of its structural resemblance to insulin.

This investigation was funded in part by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), and the clinical studies took place at the University of Florida's General Clinical Research Center funded by the Division of Research Resources (DRR).

NIADDK and DRR also supported in part the study on synthetic growth hormone releasing factor reported in the August issue of *Medical Capsules*.

- An x-ray diffraction facility is being developed at the University of Connecticut Health Center. Partially funded by the National Heart, Lung, and Blood Institute (NHLBI), this important tool for heart research is used to study what happens at the molecular level when a cardiac drug is taken.

Most cardiac drugs work by interacting with the membranes surrounding individual heart cells. Therefore "seeing" what actually goes on at that level should provide information important in designing more effective drugs to treat heart failure, angina pectoris, arrhythmias and other cardiovascular disorders.

- The initial three-year phase of a Traumatic Coma Data Bank has been completed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). The Data Bank was established to gather information for neurosurgeons who, each year, treat the 400,000 Americans who suffer head injuries.

The data gathered from six medical centers on 581 patients show that most head injuries resulting in coma are suffered by white males between the ages of 15 and 29, most often as the result of motor vehicle accidents.

A new five-year phase of the study is beginning with a larger number of patients so that more can be learned about head injuries and ways to minimize brain damage resulting from them.

More information on the Data Bank will be available soon from NINCDS.

- Researchers believe that it may now be posssible to predict with reasonable accuracy which patients are most likely to die within the first two years following a heart attack.

A study of 866 patients by the Multicenter Postinfarction Research Group, funded in part by the National Heart, Lung, and Blood Institute (NHLBI), was reported in the August 11 issue of the *New England Journal of Medicine*.

In the nine-hospital study, headed by Dr. Arthur Moss at the University of Rochester, certain measurements of cardiac function were used to predict the risk of mortality within the following two years.

One of these measurements was of the "ejection fraction," which is the proportion of blood ejected from the heart with each beat. The researchers found that the lower the "ejection fraction," the higher the mortality rate. They also looked at a second important risk indicator—frequent extra heartbeats. These are also associated with a higher death rate.

The ejection fraction, which indicates the mechanical activity of the heart, and the extra heartbeats, which show its electrical activity, provide a sensitive index of risk.

From this information, scientists hope to improve heart function by preventive measures and thereby reduce the mortality risk.

- Investigators at the Children's Nutrition Research Center at Baylor College of Medicine in Houston, funded in part by the National Institute of Child Health and Human Development (NICHD), are looking for the best nutrition for premature babies.

They are comparing the growth rates of small but healthy babies fed synthetic formula with those fed a fortified human milk preparation. This preparation consists of breast milk from the mother and additional nutrients from milk donated by other lactating women. These extra nutrients include minerals, fats and protein needed to support a growth rate comparable to what would have occurred *in utero*.

So far the two groups of infants appear to be growing at the same rate. The parents of the group of infants given fortified human milk, however, are enjoying an additional benefit of the study. Providing the milk every day gives them the opportunity to take an active role in the care of their premature babies while the infants have to remain hospitalized.

- Scientists have found that human cartilage can effectively replace malfunctioning ossicles (bones in the middle ear) to restore hearing.

Various bone and plastic substitutes for the ossicle, which transmits sound vibrations to the inner ear and then to the brain, have been tried. But the replacements were either rejected by the body or adhered to the side wall of the ear, preventing vibration.

Under a grant from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), physicians at the University of California, Davis Medical Center, have found that human cartilage can be sculptured to the proper shape and inserted in the ear under local anesthesia. Some degree of hearing is restored, even while surgery is still in progress.

Of the more than one hundred patients given this type of ossicle, most regained at least 85 percent of normal hearing, and there were no incidences of rejection after two years.

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Ms. Maureen Napper
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